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(54) Title: PROTEASE INHIBITORS

(57) Abstract

The present invention provides novel compounds of the Formula (I): A-B, its prodrug forms, or pharmaceutically acceptable salts thereof, wherein A represents a saturated, unsaturated, or a partially unsaturated bicyclic heterocyclic ring structure, and B represents an aryl or a heteroaryl group. Preferred compounds of the present invention comprise a benzimidazole or indole nucleus. The compounds of this invention are inhibitors of serine proteases, Urokinase (uPA), Factor Xa (FXa), and/or Factor VIIa (FVIIa), and have utility as anti cancer agents and/or as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals.

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PROTEASE INHIBITORS

FIELD OF INVENTION

5 The present invention relates to novel protease inhibitors.

BACKGROUND OF THE INVENTION

10 One of the most active areas in cancer research is the field of proteolytic enzymes and their role in the spread of cancer. One such class of protease that plays a significant role in the progression of cancer are the serine proteases, in particular Urokinase-type
15 plasminogen activator (uPA). Inhibitors of uPA have been postulated to be of therapeutic value in treating cancer. Inhibitors of these serine proteases also tend to be inhibitors of the closely related blood-clotting enzymes. One such blood-clotting enzyme is Factor Xa.

20 Factor Xa (herein after "FXa"), the converting enzyme of pro-thrombin to thrombin, has emerged as an alternative (to thrombin) target for drug discovery for thromboembolic disorders. A variety of compounds have been developed as potential FXa inhibitors.

25 Kunitada and Nagahara in Current Pharmaceutical Design, 1996, Vol. 2, No.5, report amidinobenzyl compounds as FXa and thrombin inhibitors. Disclosed in U.S. Patent No. 5,576,343 are aromatic amidine derivatives and salts thereof, as reversible inhibitors
30 of FXa. These compounds comprise amidino substituted indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazoyl, benzothiazolyl, naphthyl, tetrahydronaphthyl and indanyl groups, attached to a substituted phenyl ring by an alkylene group having from 1 to 4 carbon atoms.

35 In spite of the above discussed efforts, desirable treatment of cancer and thromboembolic disorders still remains elusive. There is thus a need for new compounds that will be effective in inhibiting serine proteases,

such as Urokinase, and blood-clotting enzymes such as FXa. Keeping these needs in mind, the present invention provides novel inhibitors as discussed below.

5 SUMMARY OF THE INVENTION

The present invention relates to compounds of Formula I:

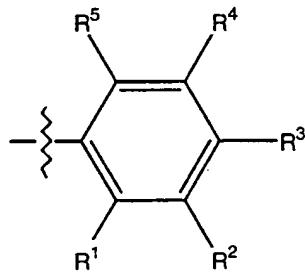
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A-B

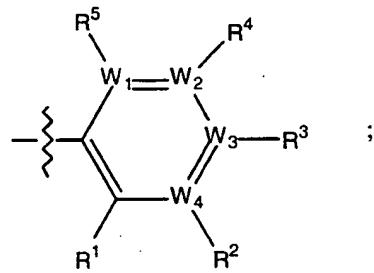
its prodrug forms, or pharmaceutically acceptable salts thereof, wherein

A represents a saturated, unsaturated, or a partially 15 unsaturated bicyclic heterocyclic ring structure substituted with R⁶, R⁷, R⁸, R⁹, and R²⁰;

B represents



or



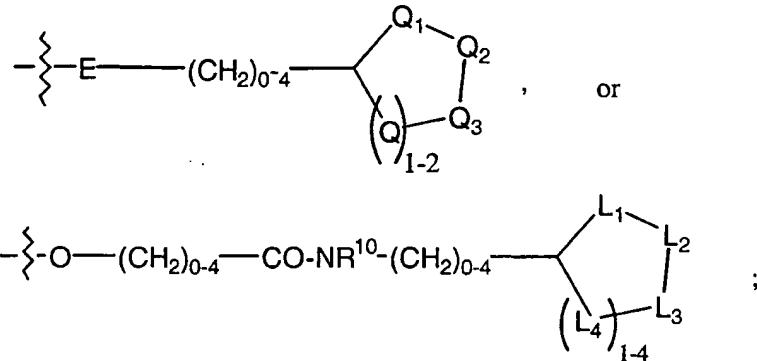
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R¹ represents OH, halogen, COOH, COO-C₁₋₄ alkyl, O-(CH₂)₀₋₁-Ph, N(R¹⁰)₂, CH₂OR¹⁰, C₁₋₆ halogenated alkyl, O-(CH₂)₁₋₄-CO-N(R¹⁰)₂, SC₁₋₄ alkyl, NHSO₂C₁₋₄ alkyl, SO₂-OH, O-SO₂-OH, O-SO₂-O-C₁₋₄ alkyl, OP(O)(OH)₂, or OPO₃C₁₋₄ alkyl;

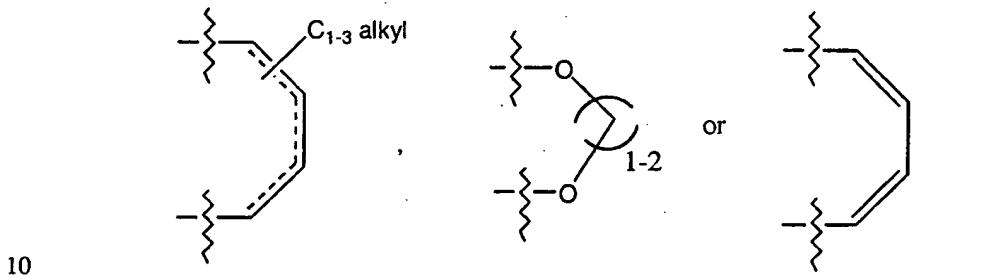
25 R², R³, R⁴, and R⁵ independently at each occurrence represent H, SH, OR¹⁰, halogen, COOR¹⁰, CONR¹¹R¹², optionally substituted aryl, optionally substituted heterocyclyl, C₁₋₁₄ cycloalkyl-C₁₋₄ alkyl, C₁₋₄ alkyl aryl, optionally substituted C₁₋₁₄ straight chain, branched or cyclo alkyl,

30 O-(CH₂)₂₋₆-NR¹⁰-(CH₂)₀₋₃-R²⁴, NR¹⁰R²⁴, (CH₂)₁₋₄-NR³³R³⁴, (CH₂)₁₋₄-COOR³³, O-(CH₂)₁₋₃-CO-het, O-(CH₂)₁₋₂-NH-CO-aryl, O-(CH₂)₁₋₂-NR¹⁰-CO-NR¹⁰R³³, O-(CH₂)₀₋₂-C(O)-NR³³R³⁴, O-(CH₂)₁₋₄-COOR¹⁰, O-(CH₂)₁₋₃-het-R³², O-optionally substituted cycloalkyl, O-(CH₂)₁₋₄-NR¹⁰-COO-t-butyl, O-(CH₂)₁₋₄-NR¹⁰R³³, O-(CH₂)₁₋₄-NR¹⁰-

C(O)-C₀₋₃-alkyl-optionally substituted aryl, O-substituted cycloalkyl, O-(CH₂)₀₋₆-optionally substituted aryl, (CH₂)₁₋₄-NH-C(O)O-(CH₂)₁₋₄-PhR¹³R¹⁴, NO₂, O-(CH₂)₀₋₄-C(O)-NH-tetrahydro carboline, NR¹⁰R²⁸, O-(CH₂)₁₋₃-optionally substituted het,
5 CH₂COOCH₃, CH=CH-COOCH₃, 5-amidino benzimidazole,



alternatively R² and R³ taken together form



10

R⁶ and R⁹ independently at each occurrence represents H, halogen, cyano, C₁₋₄ alkyl, C₁₋₄ halogenated alkyl, NO₂, O-aryl or OR¹¹;

15 R⁷ and R⁸ independently at each occurrence represent OH, CF₃, H, NO₂, C₁₋₄ alkyl, OC₁₋₄ alkyl, or O-aryl, halogen, cyano, or a basic group selected from guanidino, C(=NH)N(R¹⁰)₂, C(=NH)-NH-NH₂, C(=O)NH₂, 2-imidazoline, N-amidinomorpholine, N-amidino piperidine, 4-hydroxy-N-amidino piperidine, N-amidino pyrrolidine, tetrahydro pyrimidine, and thiazolidin-3-yl-methylideneamine; with the proviso that only one of R⁷ and R⁸ represent a basic group;

20 R¹⁰ independently at each occurrence represents H, (CH₂)₀₋₂-aryl, C₁₋₄ halo alkyl, or C₁₋₁₄ straight chain, branched or cyclo alkyl, and alternatively, when one atom is

substituted with two R¹⁰ groups, the atom along with the R¹⁰ groups can form a five to 10 membered ring structure; R¹¹ and R¹² independently at each occurrence represent H or C₁₋₄ alkyl;

5 R²⁰ represents R²⁴, C₁₋₄-alkyl, (CH₂)₁₋₃-biphenyl, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl)₂, (CH₂)₁₋₄-NH-C(O)-R²⁴, (CH₂)₁₋₄-NH-SO₂-R²⁴, halogen, COOR¹⁰, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl), (CH₂)₁₋₄-NR¹⁰-C(O)-R²⁴, (CH₂)₁₋₄-NR¹⁰-SO₂-R²⁴, (CH₂)₁₋₄-het, (CH₂)₁₋₄-CON(R¹⁰)₂, (CH₂)₁₋₄-N(R¹⁰)-C(O)-NR¹⁰R²⁴, (CH₂)₁₋₄-N(R¹⁰)-C(S)-NR¹⁰R²⁴, or (CH₂)₁₋₃-COOH;

10 R²⁴ represents R¹⁰, (CH₂)₁₋₄-optionally substituted aryl, (CH₂)₀₋₄OR¹⁰, CO-(CH₂)₁₋₂-N(R¹⁰)₂, CO(CH₂)₁₋₄-OR¹⁰, (CH₂)₁₋₄-COOR¹⁰, (CH₂)₀₋₄-N(R¹⁰)₂, SO₂R¹⁰, COR¹⁰, CON(R¹⁰)₂, (CH₂)₀₋₄-aryl-COOR¹⁰, (CH₂)₀₋₄-aryl-N(R¹⁰)₂, or (CH₂)₁₋₄-het-aryl;

15 R²⁸ represents (CH₂)₁₋₂-Ph-O-(CH₂)₀₋₂-het-R³⁰, C(O)-het, CH₂-Ph-CH₂-het-(R³⁰)₁₋₃; (CH₂)₁₋₄-cyclohexyl-R³¹, CH₂-Ph-O-Ph-(R³⁰)₁₋₂, CH₂-(CH₂OH)-het-R³⁰, CH₂-Ph-O-cycloalkyl-R³¹, CH₂-het-C(O)-CH₂-het-R³⁰, or CH₂-Ph-O-(CH₂)-O-het-R³⁰;

20 R³⁰ represents SO₂N(R¹⁰)₂, H, NHOH, amidino, or C(=NH)CH₃;

20 R³¹ represents R³⁰, amino-amidino, NH-C(=NH)CH₃, or R¹⁰;

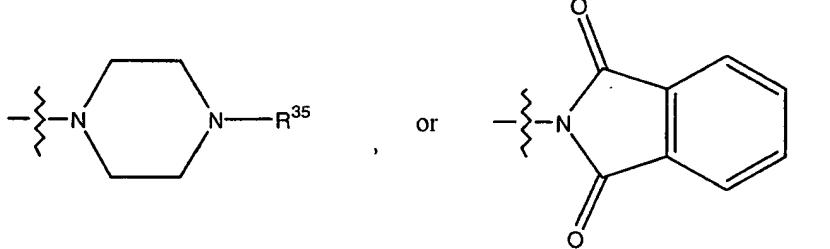
20 R³² represents H, C(O)-CH₂-NH₂, or C(O)-CH(CH(CH₃)₂)-NH₂;

20 R³³ and R³⁴ independently at each occurrence represent R¹⁰, (CH₂)₀₋₄-Ar, optionally substituted aryl, (CH₂)₀₋₄ optionally substituted heteroaryl, (CH₂)₁₋₄-CN, (CH₂)₁₋₄-N(R¹⁰)₂, (CH₂)₁₋₄-

25 OH, (CH₂)₁₋₄-SO₂-N(R¹⁰)₂;

alternatively, R³³ and R³⁴ along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-

30 isoquinoline,



R¹⁵ represents R¹⁰, SO₂-R¹⁰, COR¹⁰, or CONHR¹⁰;
E represents a bond, S(O)₀₋₂, O or NR¹⁰;
W₁, W₂, W₃ and W₄ independently represent C or N; and
Q, Q¹, Q², Q³, L¹, L², L³ and L⁴ independently at each
5 occurrence represent N-natural or unnatural amino acid
side chain, CHR¹⁰, O, NH, S(O)₀₋₂, N-C(O)-NHR¹⁰, SO₂-N(R¹⁰)₂,
N-C(O)-NH-(CH₂)₁₋₄-R²⁶, NR¹⁰, N-heteroaryl, N-C(=NH)-NHR¹⁰, or
N-C(=NH)C₁₋₄ alkyl;
R²⁶ represents OH, NH₂, or SH;
10 provided that, (i) when R¹ = OH; R⁷ = amidine; R², R⁶, R⁸,
R⁹, and R²⁰ each represent H; and R³, R⁴, R⁵ are
independently chosen from H, CH₃, and halogen, then only
one of R³, R⁴, and R⁵ represents H; (ii) when R¹ = OH; R⁷ =
amidine; R², R³, R⁴, R⁵, and R²⁰ each represent H; and R⁶,
15 R⁸, R⁹ are independently chosen from H, CH₃, and halogen,
then only one of R⁶, R⁸, and R⁹ represents H; (iii) at
least two of W₁, W₂, W₃ and W₄ represent C and at least
one of W₁, W₂, W₃ and W₄ represent N; and (iv) when R¹ = OH;
R⁷ = amidine; and R², R³, R⁴, R⁵, R⁶, R⁸, and R⁹, represent H,
20 R²⁰ cannot be CH₃.

Also provided by the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for treating or preventing a thromboembolic disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of
30 Formula I or a pharmaceutically acceptable salt thereof.

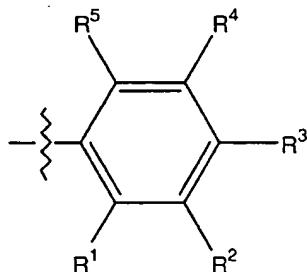
DETAILED DESCRIPTION OF THE INVENTION

Provided by the present invention is a compound of
35 Formula I:

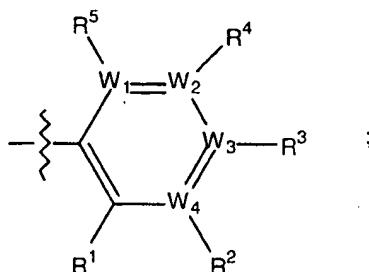
A-B

its prodrug forms, or pharmaceutically acceptable salts thereof, wherein

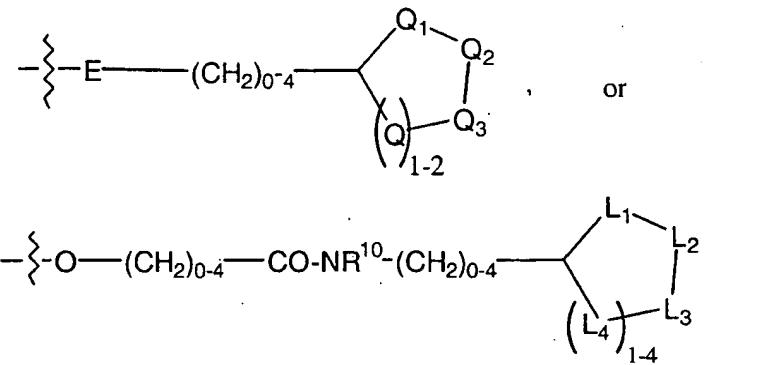
A represents a saturated, unsaturated, or a partially unsaturated bicyclic heterocyclic ring structure
5 substituted with R⁶, R⁷, R⁸, R⁹, and R²⁰;
B represents



or

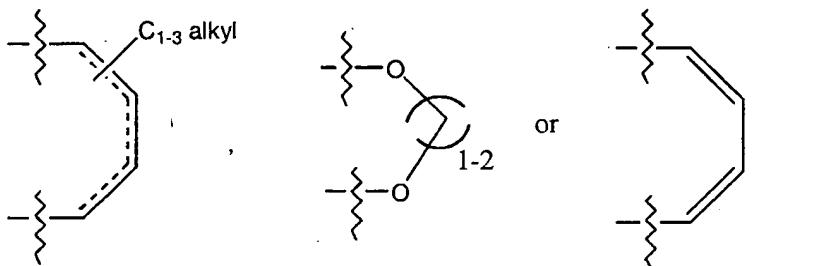


10 R¹ represents OH, halogen, COOH, COO-C₁₋₄ alkyl, O-(CH₂)₀₋₁-Ph, N(R¹⁰)₂, CH₂OR¹⁰, C₁₋₆ halogenated alkyl, O-(CH₂)₁₋₄-CO-N(R¹⁰)₂, SC₁₋₄ alkyl, NHSO₂C₁₋₄alkyl, SO₂-OH, O-SO₂-OH, O-SO₂-O-C₁₋₄ alkyl, OP(O)(OH)₂, or OPO₃C₁₋₄ alkyl;
R², R³, R⁴, and R⁵ independently at each occurrence
15 represent H, SH, OR¹⁰, halogen, COOR¹⁰, CONR¹¹R¹², optionally substituted aryl, optionally substituted heterocyclyl, C₁₋₁₄ cycloalkyl-C₁₋₄ alkyl, C₁₋₄ alkyl aryl, optionally substituted C₁₋₁₄ straight chain, branched or cyclo alkyl,
O-(CH₂)₂₋₆-NR¹⁰-(CH₂)₀₋₃-R²⁴, NR¹⁰R²⁴, (CH₂)₁₋₄-NR³³R³⁴, (CH₂)₁₋₄-COOR³³, O-(CH₂)₁₋₃-CO-het, O-(CH₂)₁₋₂-NH-CO-aryl, O-(CH₂)₁₋₂-NR¹⁰-CO-NR¹⁰R³³, O-(CH₂)₀₋₂-C(O)-NR³³R³⁴, O-(CH₂)₁₋₄-COOR¹⁰, O-(CH₂)₁₋₃-het-R³², O-optionally substituted cycloalkyl, O-(CH₂)₁₋₄-NR¹⁰-COO-t-butyl, O-(CH₂)₁₋₄-NR¹⁰R³³, O-(CH₂)₁₋₄-NR¹⁰-C(O)-C₀₋₃-alkyl-optionally substituted aryl, O-substituted
20 cycloalkyl, O-(CH₂)₀₋₆-optionally substituted aryl, (CH₂)₁₋₄-NH-C(O)O-(CH₂)₁₋₄-PhR¹³R¹⁴, NO₂, O-(CH₂)₀₋₄-C(O)-NH-tetrahydro carboline, NR¹⁰R²⁸, O-(CH₂)₁₋₃-optionally substituted het, CH₂COOCH₃, CH=CH-COOCH₃, 5-amidino benzimidazole,
25



alternatively R^2 and R^3 taken together form

5



R^6 and R^9 independently at each occurrence represents H, halogen, cyano, C_{1-4} alkyl, C_{1-4} halogenated alkyl, NO_2 , O-aryl or OR^{11} ;

10 R^7 and R^8 independently at each occurrence represent OH, CF_3 , H, NO_2 , C_{1-4} alkyl, OC_{1-4} alkyl, or O-aryl, halogen, cyano, or a basic group selected from guanidino, $C(=NH)N(R^{10})_2$, $C(=NH)-NH-NH_2$, $C(=O)NH_2$, 2-imidazoline, N-amidinomorpholine, N-amidino piperidine, 4-hydroxy-N-amidino piperidine, N-amidino pyrrolidine, tetrahydro pyrimidine, and thiazolidin-3-yl-methylideneamine; with the proviso that only one of R^7 and R^8 represent a basic group;

15

R^{10} independently at each occurrence represents H, $(CH_2)_{0-2}$ -aryl, C_{1-4} halo alkyl, or C_{1-14} straight chain, branched or cyclo alkyl, and alternatively, when one atom is substituted with two R^{10} groups, the atom along with the R^{10} groups can form a five to 10 membered ring structure;
 R^{11} and R^{12} independently at each occurrence represent H or
25 C_{1-4} alkyl;

R²⁰ represents R²⁴, C₁₋₄-alkyl, (CH₂)₁₋₃-biphenyl, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl)₂, (CH₂)₁₋₄-NH-C(O)-R²⁴, (CH₂)₁₋₄-NH-SO₂-R²⁴, halogen, COOR¹⁰, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl), (CH₂)₁₋₄-NR¹⁰-C(O)-R²⁴, (CH₂)₁₋₄-NR¹⁰-SO₂-R²⁴, (CH₂)₁₋₄-het, (CH₂)₁₋₄-CON(R¹⁰)₂, 5 (CH₂)₁₋₄-N(R¹⁰)-C(O)-NR¹⁰R²⁴, (CH₂)₁₋₄-N(R¹⁰)-C(S)-NR¹⁰R²⁴, or (CH₂)₁₋₃-COOH;

R²⁴ represents R¹⁰, (CH₂)₁₋₄-optionally substituted aryl, (CH₂)₀₋₄OR¹⁰, CO-(CH₂)₁₋₂-N(R¹⁰)₂, CO(CH₂)₁₋₄-OR¹⁰, (CH₂)₁₋₄-COOR¹⁰, (CH₂)₀₋₄-N(R¹⁰)₂, SO₂R¹⁰, COR¹⁰, CON(R¹⁰)₂, (CH₂)₀₋₄-aryl-COOR¹⁰, 10 (CH₂)₀₋₄-aryl-N(R¹⁰)₂, or (CH₂)₁₋₄-het-aryl;

R²⁸ represents (CH₂)₁₋₂-Ph-O-(CH₂)₀₋₂-het-R³⁰, C(O)-het, CH₂-Ph-CH₂-het-(R³⁰)₁₋₃; (CH₂)₁₋₄-cyclohexyl-R³¹, CH₂-Ph-O-Ph-(R³⁰)₁₋₂, CH₂-(CH₂OH)-het-R³⁰, CH₂-Ph-O-cycloalkyl-R³¹, CH₂-het-C(O)-CH₂-het-R³⁰, or CH₂-Ph-O-(CH₂)-O-het-R³⁰;

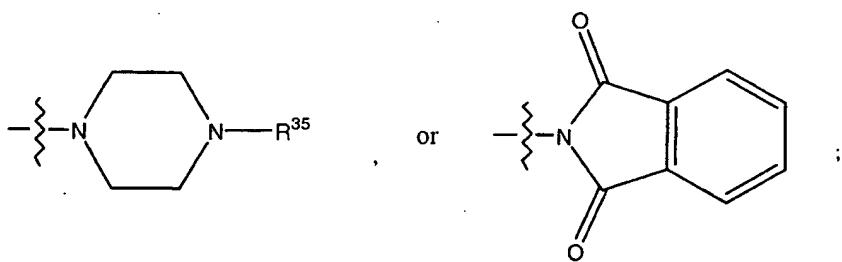
15 R³⁰ represents SO₂N(R¹⁰)₂, H, NHOH, amidino, or C(=NH)CH₃;

R³¹ represents R³⁰, amino-amidino, NH-C(=NH)CH₃, or R¹⁰;

R³² represents H, C(O)-CH₂-NH₂, or C(O)-CH(CH(CH₃)₂)-NH₂;

R³³ and R³⁴ independently at each occurrence represent R¹⁰, (CH₂)₀₋₄-Ar, optionally substituted aryl, (CH₂)₀₋₄ optionally substituted heteroaryl, (CH₂)₁₋₄-CN, (CH₂)₁₋₄-N(R¹⁰)₂, (CH₂)₁₋₄-OH, (CH₂)₁₋₄-SO₂-N(R¹⁰)₂; 20 alternatively, R³³ and R³⁴ along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-

25 Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-isoquinoline,



30 R³⁵ represents R¹⁰, SO₂-R¹⁰, COR¹⁰, or CONHR¹⁰;

E represents a bond, S(O)₀₋₂, O or NR¹⁰;

W₁, W₂, W₃ and W₄ independently represent C or N; and

Q , Q^1 , Q^2 , Q^3 , L^1 , L^2 , L^3 and L^4 independently at each occurrence represent N-natural or unnatural amino acid side chain, CHR^{10} , O , NH , $S(O)_{0-2}$, $N-C(O)-NHR^{10}$, $SO_2-N(R^{10})_2$, $N-C(O)-NH-(CH_2)_{1-4}-R^{26}$, NR^{10} , N-heteroaryl, $N-C(=NH)-NHR^{10}$, or
5 $N-C(=NH)C_{1-4}$ alkyl;

R^{26} represents OH , NH_2 , or SH ;
provided that, (i) when $R^1 = OH$; $R^7 =$ amidine; R^2 , R^6 , R^8 ,
 R^9 , and R^{20} each represent H; and R^3 , R^4 , R^5 are
independently chosen from H, CH_3 , and halogen, then only
10 one of R^3 , R^4 , and R^5 represents H; (ii) when $R^1 = OH$; $R^7 =$ amidine;
 R^2 , R^3 , R^4 , R^5 , and R^{20} each represent H; and R^6 ,
 R^8 , R^9 are independently chosen from H, CH_3 , and halogen,
then only one of R^6 , R^8 , and R^9 represents H; (iii) at
least two of W_1 , W_2 , W_3 and W_4 represent C and at least
15 one of W_1 , W_2 , W_3 and W_4 represent N; and (iv) when $R^1 = OH$;
 $R^7 =$ amidine; and R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , and R^9 , represent H,
 R^{20} cannot be CH_3 .

A preferred embodiment of the present invention provides a compound of Formula I:

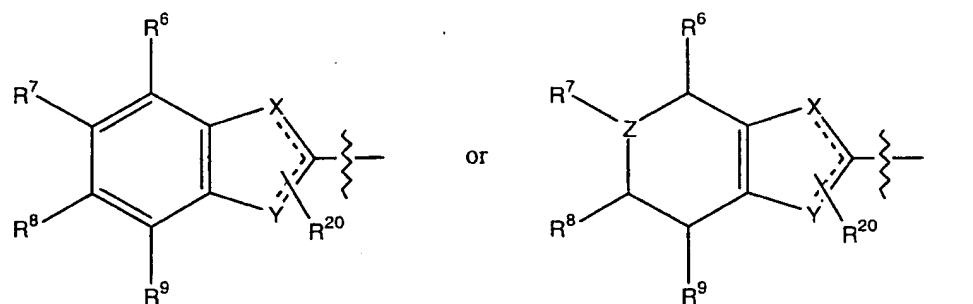
20

A-B

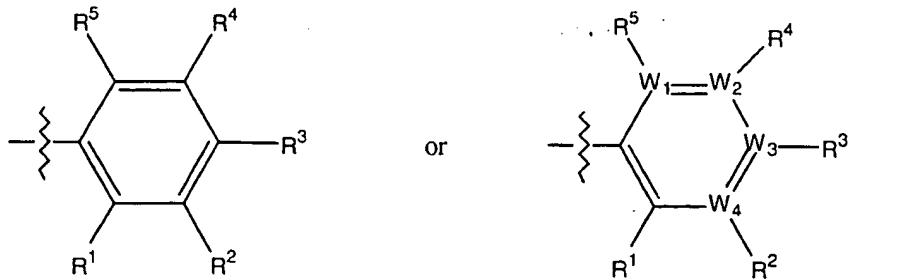
.....Formula I

its prodrug forms, or pharmaceutically acceptable salts thereof, wherein

25 A represents

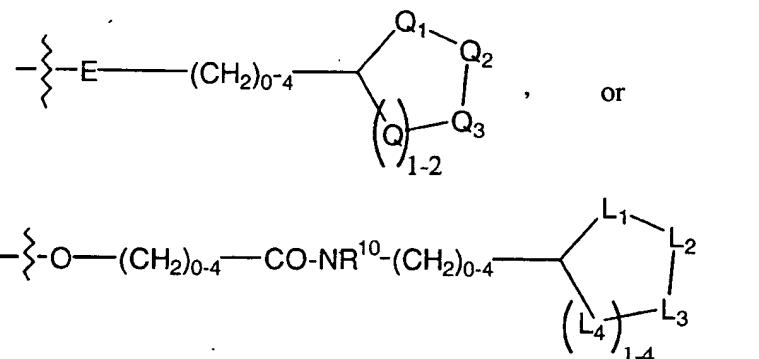


B represents

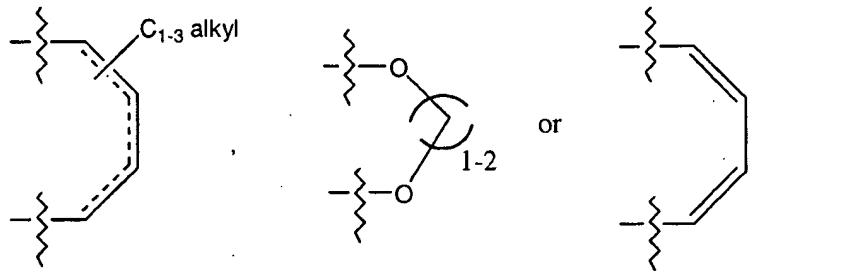


R^1 represents OH, halogen, COOH, COO-C_{1-4} alkyl, $O-(\text{CH}_2)_{0-1}-\text{Ph}$, $N(\text{R}^{10})_2$, $\text{CH}_2\text{OR}^{10}$, C_{1-6} halogenated alkyl, $O-(\text{CH}_2)_{1-4}-\text{CO-N}(\text{R}^{10})_2$, SC_{1-4} alkyl, $\text{NHSO}_2\text{C}_{1-4}$ alkyl, SO_2-OH , $O-\text{SO}_2-\text{OH}$, $O-\text{SO}_2-\text{O-C}_{1-4}$ alkyl, OP(O)(OH)_2 , or $\text{OPO}_3\text{C}_{1-4}$ alkyl;

R^2 , R^3 , R^4 , and R^5 independently at each occurrence represent H, SH, OR^{10} , halogen, COOR^{10} , $\text{CONR}^{11}\text{R}^{12}$, optionally substituted aryl, optionally substituted heterocyclyl, C_{4-14} cycloalkyl- C_{1-4} alkyl, C_{1-4} alkyl aryl, optionally substituted C_{1-14} straight chain, branched or cyclo alkyl, $O-(\text{CH}_2)_{2-6}-\text{NR}^{10}-\text{(CH}_2)_{0-3}-\text{R}^{24}$, $\text{NR}^{10}\text{R}^{24}$, $(\text{CH}_2)_{1-4}-\text{NR}^{33}\text{R}^{34}$, $(\text{CH}_2)_{1-4}-\text{COOR}^{33}$, $O-(\text{CH}_2)_{1-3}-\text{CO-het}$, $O-(\text{CH}_2)_{1-2}-\text{NH-CO-aryl}$, $O-(\text{CH}_2)_{1-2}-\text{NR}^{10}-\text{CO-NR}^{10}\text{R}^{33}$, $O-(\text{CH}_2)_{0-2}-\text{C(O)-NR}^{33}\text{R}^{34}$, $O-(\text{CH}_2)_{1-4}-\text{COOR}^{10}$, $O-(\text{CH}_2)_{1-3}-\text{het-R}^{32}$, O-optionally substituted cycloalkyl, $O-(\text{CH}_2)_{1-4}-\text{NR}^{10}-\text{COO-t-butyl}$, $O-(\text{CH}_2)_{1-4}-\text{NR}^{10}\text{R}^{33}$, $O-(\text{CH}_2)_{1-4}-\text{NR}^{10}-\text{C(O)-C}_{0-3}-\text{alkyl}$ -optionally substituted aryl, O-substituted cycloalkyl, $O-(\text{CH}_2)_{0-6}$ -optionally substituted aryl, $(\text{CH}_2)_{1-4}-\text{NH-C(O)O-(CH}_2)_{1-4}-\text{PhR}^{13}\text{R}^{14}$, NO_2 , $O-(\text{CH}_2)_{0-4}-\text{C(O)-NH-tetrahydrocarboline}$, $\text{NR}^{10}\text{R}^{28}$, $O-(\text{CH}_2)_{1-3}$ -optionally substituted het, $\text{CH}_2\text{COOCH}_3$, CH=CH-COOCH_3 , 5-amidino benzimidazole,



alternatively R^2 and R^3 taken together form



R^6 and R^9 independently at each occurrence represents H, halogen, cyano, C_{1-4} alkyl, C_{1-4} halogenated alkyl, NO_2 , O-aryl or OR^{11} ;

R^7 and R^8 independently at each occurrence represent OH, CF_3 , H, NO_2 , C_{1-4} alkyl, OC_{1-4} alkyl, or O-aryl, halogen, cyano, or a basic group selected from guanidino, $C(=NH)N(R^{10})_2$, $C(=NH)-NH-NH_2$, $C(=O)NH_2$, 2-imidazoline, N-amidinomorpholine, N-amidino piperidine, 4-hydroxy-N-amidino piperidine, N-amidino pyrrolidine, tetrahydro pyrimidine, and thiazolidin-3-yl-methylideneamine; with the proviso that only one of R^7 and R^8 represent a basic group;

R^{10} independently at each occurrence represents H, $(CH_2)_{0-2}$ -aryl, C_{1-4} halo alkyl, or C_{1-14} straight chain, branched or cyclo alkyl, and alternatively, when one atom is substituted with two R^{10} groups, the atom along with the R^{10} groups can form a five to 10 membered ring structure;

R^{11} and R^{12} independently at each occurrence represent H or C_{1-4} alkyl;

R^{24} represents R^{24} , C_{1-4} -alkyl, $(CH_2)_{1-3}$ -biphenyl, $(CH_2)_{1-4}$ -Ph- $N(SO_2-C_{1-2}-alkyl)_2$, $(CH_2)_{1-4}$ -NH-C(O)- R^{24} , $(CH_2)_{1-4}$ -NH-SO₂- R^{24} , halogen, COOR¹⁰, $(CH_2)_{1-4}$ -Ph-N(SO₂-C₁₋₂-alkyl), $(CH_2)_{1-4}$ -NR¹⁰-

$C(O)-R^{24}$, $(CH_2)_{1-4}$ -NR¹⁰-SO₂- R^{24} , $(CH_2)_{1-4}$ -het, $(CH_2)_{1-4}$ -CON(R¹⁰)₂, $(CH_2)_{1-4}$ -N(R¹⁰)-C(O)-NR¹⁰R²⁴, $(CH_2)_{1-4}$ -N(R¹⁰)-C(S)-NR¹⁰R²⁴, or $(CH_2)_{1-3}$ -COOH;

R^{24} represents R^{10} , $(CH_2)_{1-4}$ -optionally substituted aryl, $(CH_2)_{0-4}OR^{10}$, CO-(CH₂)₁₋₂-N(R¹⁰)₂, CO(CH₂)₁₋₄-OR¹⁰, $(CH_2)_{1-4}$ -COOR¹⁰, $(CH_2)_{0-4}$ -N(R¹⁰)₂, SO₂R¹⁰, COR¹⁰, CON(R¹⁰)₂, $(CH_2)_{0-4}$ -aryl-COOR¹⁰, $(CH_2)_{0-4}$ -aryl-N(R¹⁰)₂, or $(CH_2)_{1-4}$ -het-aryl;

R^{28} represents $(CH_2)_{1-2}$ -Ph-O-(CH₂)₀₋₂-het-R³⁰, C(O)-het, CH₂-Ph-CH₂-het-(R³⁰)₁₋₃; $(CH_2)_{1-4}$ -cyclohexyl-R³¹, CH₂-Ph-O-Ph-(R³⁰)₁₋₂,

$\text{CH}_2\text{-}(\text{CH}_2\text{OH})\text{-het-R}^{30}$, $\text{CH}_2\text{-Ph-O-cycloalkyl-R}^{31}$, $\text{CH}_2\text{-het-C(O)-CH}_2\text{-het-R}^{30}$, or $\text{CH}_2\text{-Ph-O-(CH}_2\text{)-O-het-R}^{30}$;

R^{30} represents $\text{SO}_2\text{N(R}^{10}\text{)}_2$, H, NHOH, amidino, or C(=NH)CH_3 ;

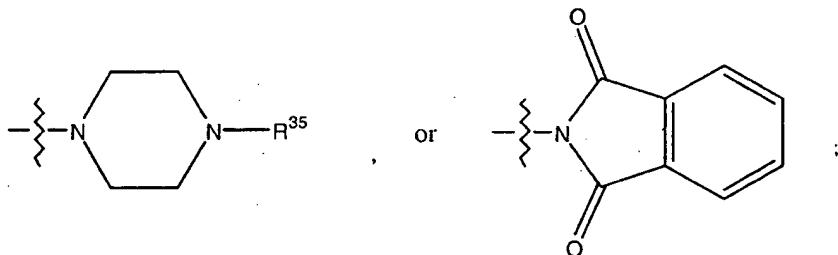
R^{31} represents R^{30} , amino-amidino, NH-C(=NH)CH_3 , or R^{10} ;

5 R^{32} represents H, $\text{C(O)-CH}_2\text{-NH}_2$, or $\text{C(O)-CH(CH(CH}_3\text{)}_2\text{-NH}_2$;

R^{33} and R^{34} independently at each occurrence represent R^{10} , $(\text{CH}_2)_{0-4}\text{-Ar}$, optionally substituted aryl, $(\text{CH}_2)_{0-4}$ optionally substituted heteroaryl, $(\text{CH}_2)_{1-4}\text{-CN}$, $(\text{CH}_2)_{1-4}\text{-N(R}^{10}\text{)}_2$, $(\text{CH}_2)_{1-4}\text{-OH}$, $(\text{CH}_2)_{1-4}\text{-SO}_2\text{-N(R}^{10}\text{)}_2$;

10 alternatively, R^{33} and R^{34} along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-isoquinoline,

15



R^{35} represents R^{10} , $\text{SO}_2\text{-R}^{10}$, COR^{10} , or CONHR^{10} ;

E represents a bond, S(O)_{0-2} , O or NR^{10} ;

20 W_1 , W_2 , W_3 and W_4 independently represent C or N; and Q , Q^1 , Q^2 , Q^3 , L^1 , L^2 , L^3 and L^4 independently at each occurrence represent N-natural or unnatural amino acid side chain, CHR^{10} , O, NH, S(O)_{0-2} , N-C(O)-NHR^{10} , $\text{SO}_2\text{-N(R}^{10}\text{)}_2$, $\text{N-C(O)-NH-(CH}_2\text{)}_{1-4}\text{-R}^{26}$, NR^{10} , N-heteroaryl, N-C(=NH)-NHR^{10} , or 25 N-C(=NH)C_{1-4} alkyl;

R^{26} represents OH, NH_2 , or SH;

provided that, (i) when $R^1 = \text{OH}$; $R^7 = \text{amidine}$; R^2 , R^6 , R^8 , R^9 , and R^{20} each represent H; and R^3 , R^4 , R^5 are independently chosen from H, CH_3 , and halogen, then only

30 one of R^3 , R^4 , and R^5 represents H; (ii) when $R^1 = \text{OH}$; $R^7 = \text{amidine}$; R^2 , R^3 , R^4 , R^5 , and R^{20} each represent H; and R^6 , R^8 , R^9 are independently chosen from H, CH_3 , and halogen, then only one of R^6 , R^8 , and R^9 represents H; (iii) at

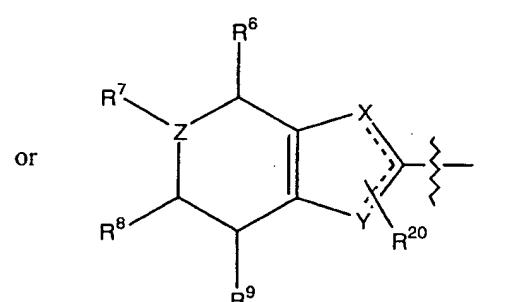
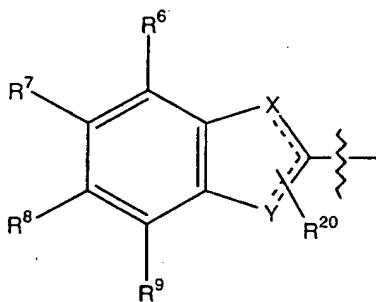
least two of W_1 , W_2 , W_3 and W_4 represent C and at least one of W_1 , W_2 , W_3 and W_4 represent N; and (iv) when R^1 = OH; R^7 = amidine; and R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , and R^9 , represent H, R^{20} cannot be CH_3 .

5 A further preferred embodiment provides a compound of Formula I wherein:

A-B

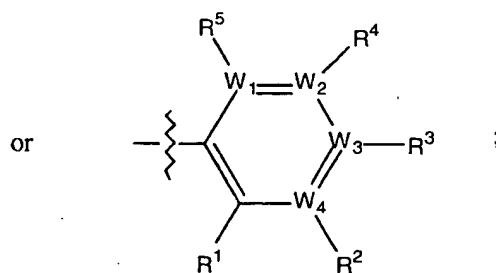
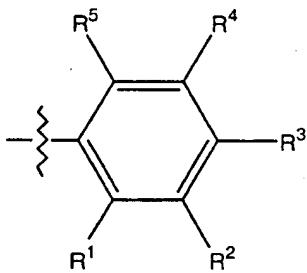
its prodrug forms, or pharmaceutically acceptable salts
10 thereof, wherein

A represents



B represents

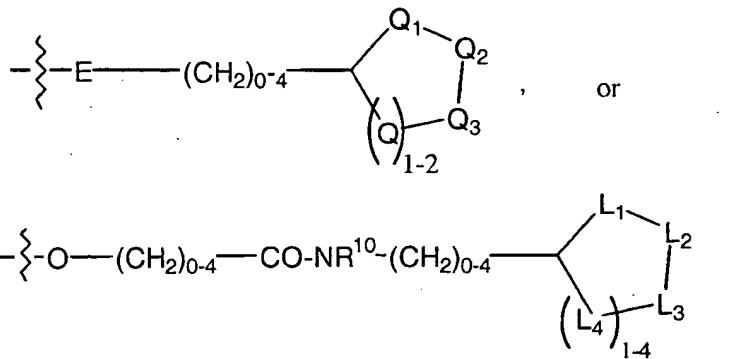
15



R^1 represents OH, halogen, COOH, $COO-C_{1-4}$ alkyl, $O-(CH_2)_{0-1}-Ph$, $N(R^{10})_2$, CH_2OR^{10} , C_{1-6} halogenated alkyl, $O-(CH_2)_{1-4}-CO-N(R^{10})_2$, SC_{1-4} alkyl, $NHSO_2C_{1-4}$ alkyl, SO_2-OH , $O-SO_2-OH$, $O-SO_2-O-C_{1-4}$ alkyl, $OP(O)(OH)_2$, or OPO_3C_{1-4} alkyl;
20

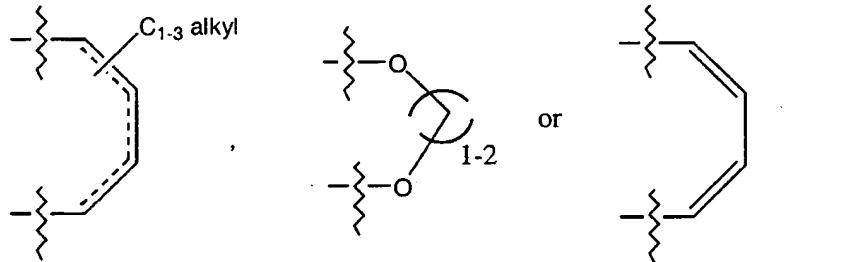
R^2 , R^3 , R^4 , and R^5 independently at each occurrence represent H, SH, OR^{10} , halogen, $COOR^{10}$, $CONR^{11}R^{12}$, optionally substituted aryl, optionally substituted heterocyclyl, C_{4-24} cycloalkyl- C_{1-4} alkyl, C_{1-4} alkyl aryl, optionally substituted C_{1-14} straight chain, branched or cyclo alkyl, $O-(CH_2)_{2-6}-NR^{10}-(CH_2)_{0-3}-R^{24}$, $NR^{10}R^{24}$, $(CH_2)_{1-4}-NR^{33}R^{34}$, $(CH_2)_{1-4}-$

COOR^{33} , $\text{O}-(\text{CH}_2)_{1-3}-\text{CO-het}$, $\text{O}-(\text{CH}_2)_{1-2}-\text{NH-CO-aryl}$, $\text{O}-(\text{CH}_2)_{1-2}-\text{NR}^{10}-\text{CO-NR}^{10}\text{R}^{33}$, $\text{O}-(\text{CH}_2)_{0-2}-\text{C(O)-NR}^{33}\text{R}^{34}$, $\text{O}-(\text{CH}_2)_{1-4}-\text{COOR}^{10}$, $\text{O}-(\text{CH}_2)_{1-3}-\text{het-R}^{32}$, O -optionally substituted cycloalkyl, $\text{O}-(\text{CH}_2)_{1-4}-\text{NR}^{10}-\text{COO-t-butyl}$, $\text{O}-(\text{CH}_2)_{1-4}-\text{NR}^{10}\text{R}^{33}$, $\text{O}-(\text{CH}_2)_{1-4}-\text{NR}^{10}-\text{C(O)-C}_{0-3}-\text{alkyl}$ -optionally substituted aryl, O -substituted cycloalkyl, $\text{O}-(\text{CH}_2)_{0-6}$ -optionally substituted aryl, $(\text{CH}_2)_{1-4}-\text{NH-C(O)O}-(\text{CH}_2)_{1-4}-\text{PhR}^{13}\text{R}^{14}$, NO_2 , $\text{O}-(\text{CH}_2)_{0-4}-\text{C(O)-NH-tetrahydro carboline}$, $\text{NR}^{10}\text{R}^{28}$, $\text{O}-(\text{CH}_2)_{1-3}$ -optionally substituted het, $\text{CH}_2\text{COOCH}_3$, CH=CH-COOCH_3 , 5-amidino benzimidazole,



10

alternatively R^2 and R^3 taken together form



15

R^6 and R^9 independently at each occurrence represents H, halogen, cyano, C_{1-4} alkyl, C_{1-4} halogenated alkyl, NO_2 , O-aryl or OR^{11} ;

R^7 and R^8 independently at each occurrence represent OH, CF_3 , H, NO_2 , C_{1-4} alkyl, OC_{1-4} alkyl, or O-aryl, halogen, cyano, or a basic group selected from guanidino, $\text{C}(\text{=NH})\text{N}(\text{R}^{10})_2$, $\text{C}(\text{=NH})-\text{NH-NH}_2$, $\text{C}(\text{=O})\text{NH}_2$, 2-imidazoline, N-amidinomorpholine, N-amidino piperidine, 4-hydroxy-N-amidino piperidine, N-amidino pyrrolidine, tetrahydro pyrimidine, and thiazolidin-3-yl-methylideneamine; with

the proviso that only one of R⁷ and R⁸ represent a basic group;

R¹⁰ independently at each occurrence represents H, (CH₂)₀₋₂-aryl, C₁₋₄ halo alkyl, or C₁₋₁₄ straight chain, branched or

5 cyclo alkyl, and alternatively, when one atom is substituted with two R¹⁰ groups, the atom along with the R¹⁰ groups can form a five to 10 membered ring structure;

R¹¹ and R¹² independently at each occurrence represent H or C₁₋₄ alkyl;

10 R²⁰ represents R²⁴, C₁₋₄-alkyl, (CH₂)₁₋₃-biphenyl, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl)₂, (CH₂)₁₋₄-NH-C(O)-R²⁴, (CH₂)₁₋₄-NH-SO₂-R²⁴, halogen, COOR¹⁰, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl), (CH₂)₁₋₄-NR¹⁰-C(O)-R²⁴, (CH₂)₁₋₄-NR¹⁰-SO₂-R²⁴, (CH₂)₁₋₄-het, (CH₂)₁₋₄-CON(R¹⁰)₂, (CH₂)₁₋₄-N(R¹⁰)-C(O)-NR¹⁰R²⁴, (CH₂)₁₋₄-N(R¹⁰)-C(S)-NR¹⁰R²⁴, or

15 (CH₂)₁₋₃-COOH;

R²⁴ represents R¹⁰, (CH₂)₁₋₄-optionally substituted aryl, (CH₂)₀₋₄OR¹⁰, CO-(CH₂)₁₋₂-N(R¹⁰)₂, CO(CH₂)₁₋₄-OR¹⁰, (CH₂)₁₋₄-COOR¹⁰, (CH₂)₀₋₄-N(R¹⁰)₂, SO₂R¹⁰, COR¹⁰, CON(R¹⁰)₂, (CH₂)₀₋₄-aryl-COOR¹⁰, (CH₂)₀₋₄-aryl-N(R¹⁰)₂, or (CH₂)₁₋₄-het-aryl;

20 R²⁸ represents (CH₂)₁₋₂-Ph-O-(CH₂)₀₋₂-het-R³⁰, C(O)-het, CH₂-Ph-CH₂-het-(R³⁰)₁₋₃; (CH₂)₁₋₄-cyclohexyl-R³¹, CH₂-Ph-O-Ph-(R³⁰)₁₋₂, CH₂-(CH₂OH)-het-R³⁰, CH₂-Ph-O-cycloalkyl-R³¹, CH₂-het-C(O)-CH₂-het-R³⁰, or CH₂-Ph-O-(CH₂)-O-het-R³⁰;

R³⁰ represents SO₂N(R¹⁰)₂, H, NHOH, amidino, or C(=NH)CH₃;

25 R³¹ represents R³⁰, amino-amidino, NH-C(=NH)CH₃, or R¹⁰;

R³² represents H, C(O)-CH₂-NH₂, or C(O)-CH(CH(CH₃)₂)-NH₂;

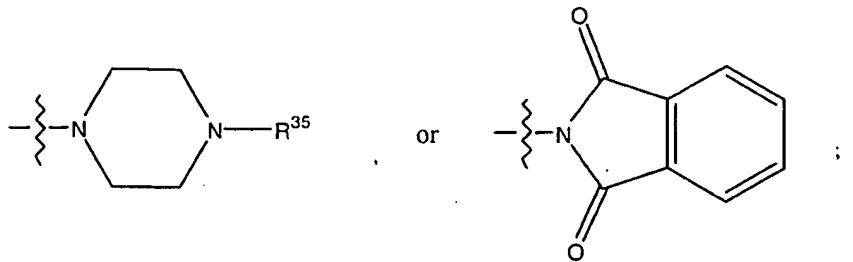
R³³ and R³⁴ independently at each occurrence represent R¹⁰, (CH₂)₀₋₄-Ar, optionally substituted aryl, (CH₂)₀₋₄ optionally substituted heteroaryl, (CH₂)₁₋₄-CN, (CH₂)₁₋₄-N(R¹⁰)₂, (CH₂)₁₋₄-

30 OH, (CH₂)₁₋₄-SO₂-N(R¹⁰)₂;

alternatively, R³³ and R³⁴ along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted

1,2,3,4-tetrahydro-

35 isoquinoline,



R^{35} represents R^{10} , SO_2-R^{10} , COR^{10} , or $CONHR^{10}$;

E represents a bond, $S(O)_{0-2}$, O or NR^{10} ;

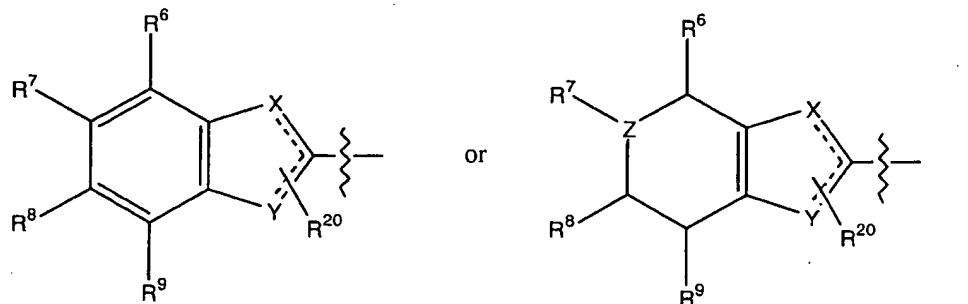
5 W_1 , W_2 , W_3 and W_4 independently represent C or N; and
 Q , Q^1 , Q^2 , Q^3 , L^1 , L^2 , L^3 and L^4 independently at each occurrence represent N-natural or unnatural amino acid side chain, CHR^{10} , O , NH , $S(O)_{0-2}$, $N-C(O)-NHR^{10}$, $SO_2-N(R^{10})_2$,
 $N-C(O)-NH-(CH_2)_{1-4}-R^{26}$, NR^{10} , N-heteroaryl, $N-C(=NH)-NHR^{10}$, or
10 $N-C(=NH)C_{1-4}$ alkyl;

R^{26} represents OH , NH_2 , or SH ;

provided that, (i) when $R^1 = OH$; $R^7 =$ amidine; R^2 , R^6 , R^8 , R^9 , and R^{20} each represent H; and R^3 , R^4 , R^5 are independently chosen from H, CH_3 , and halogen, then only
15 one of R^3 , R^4 , and R^5 represents H; (ii) when $R^1 = OH$; $R^7 =$ amidine; R^2 , R^3 , R^4 , R^5 , and R^{20} each represent H; and R^6 , R^8 , R^9 are independently chosen from H, CH_3 , and halogen, then only one of R^6 , R^8 , and R^9 represents H; (iii) at least two of W_1 , W_2 , W_3 and W_4 represent C and at least
20 one of W_1 , W_2 , W_3 and W_4 represent N; and (iv) when $R^1 = OH$; $R^7 =$ amidine; and R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , and R^9 , represent H, R^{20} cannot be CH_3 .

A further preferred embodiment provides a compound of Formula I wherein,

25 A represents



R¹ represents OH, O-Ph, COOH, or P(O)(OH)₂;

R⁷ represents H, Br, CONH₂, CN, C(=NH)-NH-NH₂, NH-C(=NH)-NH₂ or C(=NH)-NH₂;

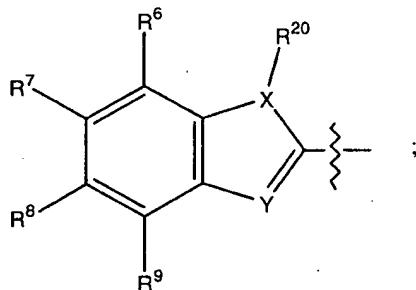
R²⁰ represents H, C₁₋₂ alkyl, (CH₂)₁₋₄-optionally substituted aryl, (CH₂)₁₋₄-het; (CH₂)₁₋₄-N(R¹⁰)₂, (CH₂)₁₋₄-CON(R¹⁰)₂, (CH₂)₁₋₄-NR¹⁰-C(O)-R²⁴, (CH₂)₁₋₄-NR¹⁰-SO₂-R²⁴, or (CH₂)₁₋₃-COOH;

X and Y independently at each occurrence are selected from NH, N, C, or CH, such that at least one of X and Y always represents N or NH; and

Z represents C or N;

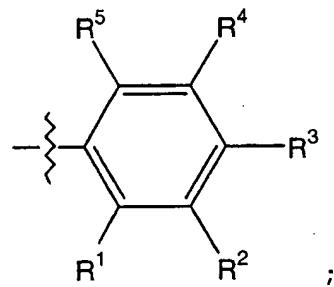
provided that, (i) when Z represents N, R⁷ represents H or C(=NH)NH₂.

Another further preferred embodiment is one wherein A represents



B represents

20



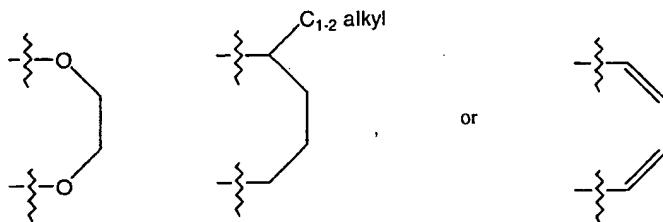
X and Y represent N; and

R⁷ represents -CONH₂, or C(=NH)-NH₂.

25 Another preferred embodiment provides a compound of Formula I wherein

R¹ represents OH, -COOH, and O-P(O)(OH)₂;

R² and R³ independently represent halogen, H, C₁₋₄ alkyl, Ph, toluyl, OH, O-(CH₂)₁₋₃-C(O)-NH-(CH₂)₁₋₂-CN, O-(CH₂)₁₋₃-Ph-p-OCH₃, O-CH₂-C(O)-NH-(CH₂)₁₋₂-CH-(CH₃)₂, O-CH₂-C(O)-NH-(CH₂)-Ph, O-CH₂-C(O)-NH-(CH₂)-Ph-pCH₃, O-C₁₋₃ alkyl, O-(CH₂)₀₋₂-Ph-R¹⁰, O-CH₂-C(O)-NH-(CH₂)₂-H, Ph-C₁₋₃ alkyl, Ph-N(R¹⁰)₂, O-(CH₂)₁₋₃-het, O-(CH₂)₁₋₃-Ph-halo, O-(CH₂)₁₋₃-NHSO₂Ph-R¹⁰, O-(CH₂)₁₋₃-NHCO-(CH₂)₀₋₂-Ph, O-CH₂-C(O)-NH-CH₂-COO-C(CH₃)₃, O-(CH₂)₂-NHC(O)-CH₂-NH₂, -OPh, O-(CH₂)₁₋₃-NH-het, O-(CH₂)₂-NH-C(O)-pyridyl, O-(CH₂)₂-NH-C(O)-NH-benzyl, O-(CH₂)₂-cyclohexyl, O-(CH₂)₂-NH-C(O)-(CH₂)₂-CONH₂, O-(CH₂)₂-NH-C(O)-CH₂-OCH₃, thiophene, pyridyl, or O-(CH₂)₂-pyridyl; alternatively R² and R³ taken together form



15

R⁴ represents halogen, H, NO₂, C₁₋₂-alkyl, CH=CH-COOCH₃, NHSO₂C₁₋₂ alkyl, NHCO-het, (CH₂)₁₋₃-COOR¹⁰, (CH₂)₁₋₃-CONH-(CH₂)₁₋₃-pyridyl, or (CH₂)₁₋₃-CONH-(CH₂)₁₋₃-dichlorophenyl;

R⁵ represents H;

20 R⁶ represents H;

R⁷ represents C(=NH)-NH₂ or NH(=NH)NH₂;

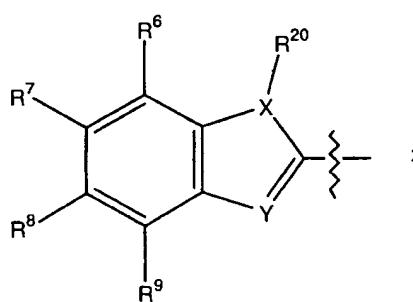
R⁸ represents H, halogen, OR¹⁰, CF₃, or C(=NH)-NH₂;

R⁹ represents H or halogen; and

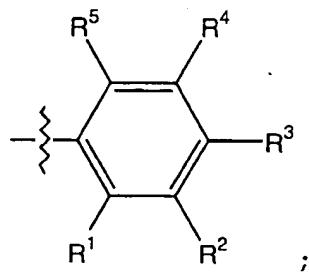
R²⁰ represents H.

25 Yet another preferred embodiment is one wherein

A represents



B represents



5

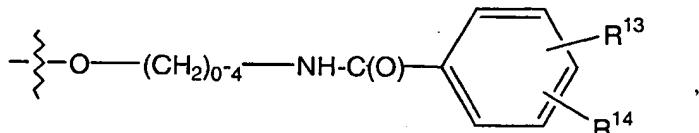
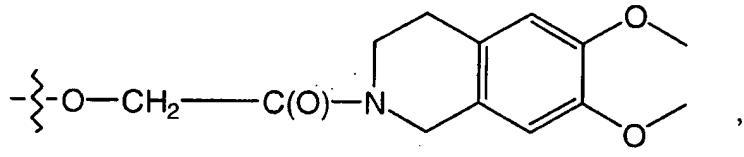
X and Y represent N.

A particularly preferred embodiment provides a compound of Formula I wherein:

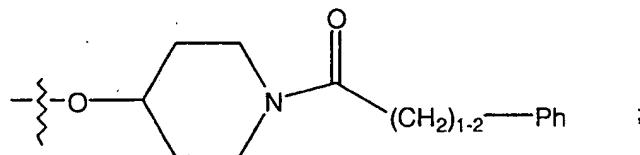
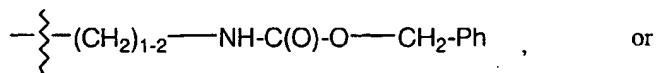
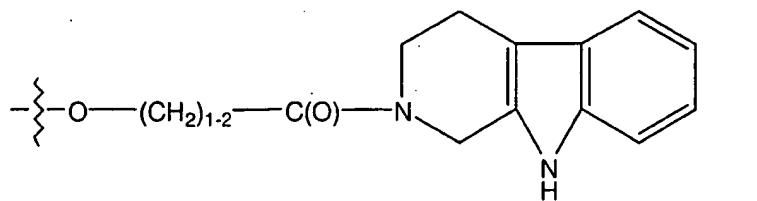
R¹ represents OH, or COOH;

10 R² represents H, halogen, OH, phenyl, O-(CH₂)₁₋₃-Ph, imidazolyl, 5-amidino benzimidazolyl, O-(CH₂)₁₋₂-C(O)-NH-C₁₋₆ alkyl, or O-CH₂-C(O)-NH-CH₂-Ph;

15 R³ represents H, O-CH₂-COOH, O-CH₂-C(O)O-C₂H₅, O-CH₂-C(O)-NH-(CH₂)₁₋₄-aryl, O-(CH₂)₁₋₄-NH-C(O)-naphthyl, CONH₂, O-(CH₂)₁₋₂-C(O)N(R¹⁰)-(CH₂)₁₋₃-Ph-R¹³R¹⁴, O-CH₂-C(O)-N(R¹⁰)-CH₂-piperanyl, O-CH₂-C(O)-NH-CH₂-indoyl, (CH₂)₀₋₄-aryl,

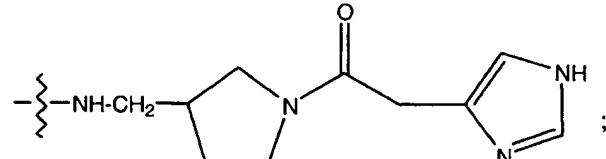
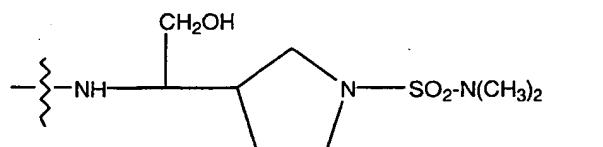
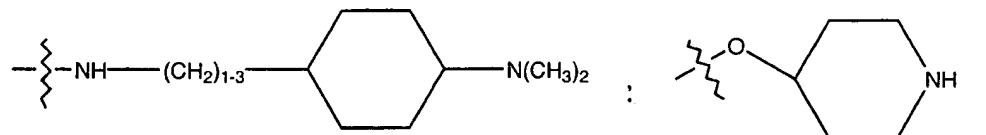
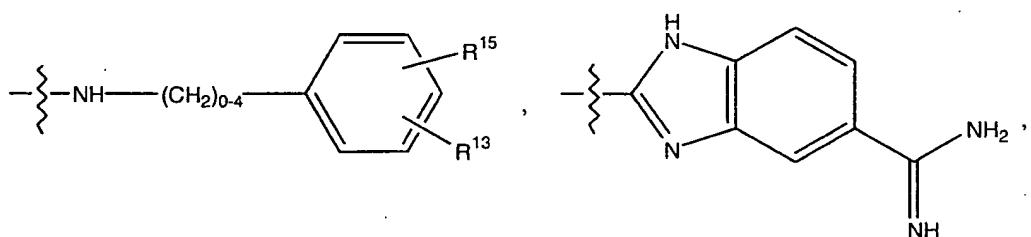


20



R^4 represents H, -CH₃, halogen, -OCH₃, -(CH₂)₁₋₂COOR¹⁰, -COOH, -NO₂, -OH, aryl,

5



R^5 represents H;

R^6 represents H;

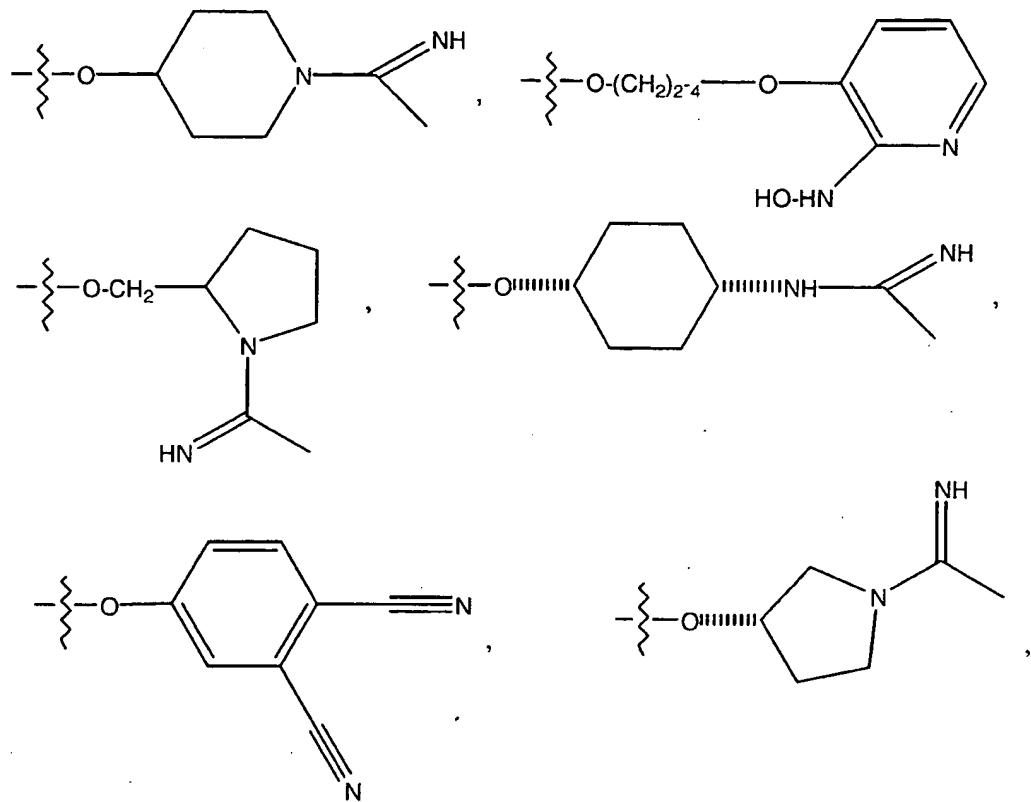
10 R^7 represents H, halogen, -C(O)-NH₂, -C(=NH)-NH₂;

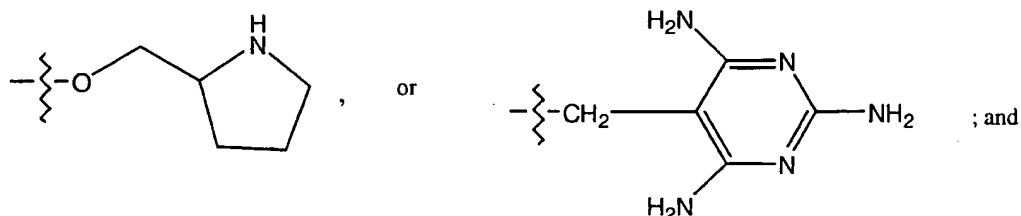
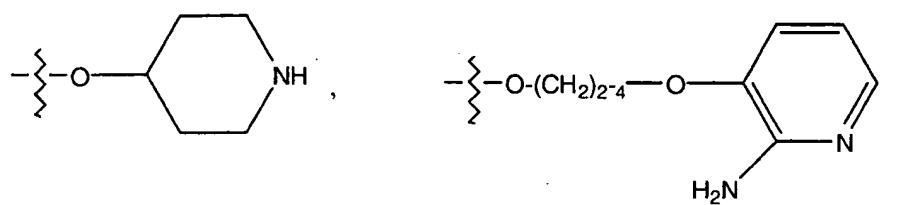
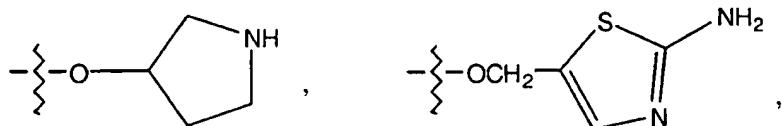
R⁸ represents H, Cl, F, OH or OCH₃;

R⁹ represents H;

R¹³ and R¹⁴ independently at each occurrence represents H, halogen, -OC₁₋₂ alkyl, -OH, -CF₃, or -C₁₋₄ alkyl; and

5 R¹⁵ represents H,

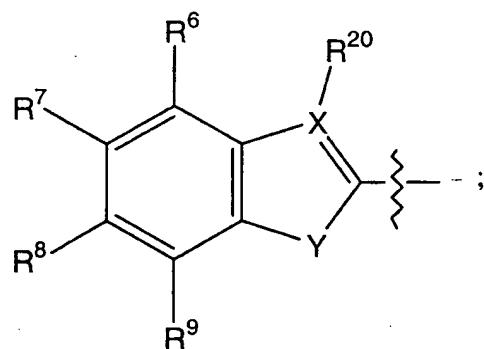




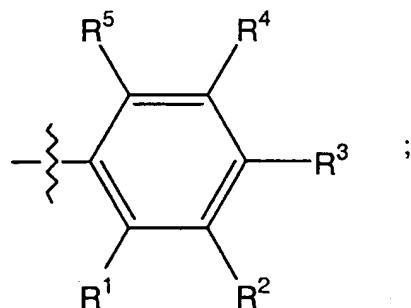
R^{20} represents H or -CH₂-Ph.

Provided in another aspect of the present invention is a compound of Formula I wherein A represents

5



B represents



X represents C; and

10 Y represents NH.

A preferred embodiment of this aspect of the present invention provides compounds wherein

R¹ represents -OH, -COOH, or P(O)(OH);

R² represents H, halogen, R¹⁰, -aryl, heteroaryl, -C₁₋₂-alkyl, COOH, -OC₁₋₂-alkyl, -O-(CH₂)₀₋₂-aryl, or -C₆₋₁₀ aryl-C₁₋₄ alkyl;

R³ represents H or -O-(CH₂)₁₋₃-COOH;

alternatively R² and R³ taken together represent



R⁴ represents H, -C₁₋₄ alkyl, -(CH₂)₁₋₄-COOH, -(CH₂)₁₋₄-COOC₁₋₂-alkyl, halogen, -(CH₂)₁₋₂-CONH₂, -CONH₂, -NO₂, -O-C₁₋₂ alkyl, or -OH;

R⁵ represents H, -C₁₋₃ alkyl, -(CH₂)₁₋₄-C(O)-NH-(CH₂)₁₋₃-heteroaryl, -(CH₂)₁₋₄-C(O)-NH-CH₃, or -COOH;

R⁶ represents H, halogen, or -C₁₋₃ alkyl;

R⁷ represents -C(O)-NH₂, -C(=NH)-NH-NH₂, or amidino;

R⁸ represents H, or halogen; and

R²⁰ represents H, -(CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂alkyl), -(CH₂)₁₋₄-NR¹⁰-C(O)-R²⁴, -(CH₂)₁₋₄-NR¹⁰-SO₂-R²⁴, -(CH₂)₁₋₄-het, -(CH₂)₁₋₄-

CON(R¹⁰)₂, -(CH₂)₁₋₄-N(R¹⁰)-C(O)-NR¹⁰R²⁴, -(CH₂)₁₋₂-Ph-NH₂, -(CH₂)₁₋₂-Ph-NO₂, -(CH₂)₁₋₄-N(R¹⁰)-C(S)-NR¹⁰R²⁴, -C₁₋₂-alkyl, -(CH₂)₁₋₄-optionally substituted aryl, -(CH₂)₁₋₄-het; -(CH₂)₁₋₃-N(R¹⁰)₂; -(CH₂)₁₋₄-CON(R¹⁰)₂, or -(CH₂)₁₋₃-COOH.

Specifically preferred compounds of the present invention are selected from

3-[3-Bromo-5-(6-carbamimidoyl-1H-benzoimidazol-2-yl)-4-hydroxy-phenyl]-N-phenethyl-propionamide;

3-[4-(6-Carbamimidoyl-1H-benzoimidazol-2-yl)-3-hydroxy-phenyl]-N-(2,3-dichloro-benzyl)-propionamide;

2-[4-(6-Carbamimidoyl-1H-benzoimidazol-2-yl)-3-hydroxy-phenoxy]-N-(2,3-dichloro-benzyl)-acetamide;

3-[3-Bromo-5-(6-carbamimidoyl-1H-benzoimidazol-2-yl)-4-hydroxy-phenyl]-N-[2-(2,4-dichloro-phenyl)-ethyl]-propionamide;

3-[3-Bromo-5-(6-carbamimidoyl-1H-benzoimidazol-2-yl)-4-hydroxy-phenyl]-N-(2-pyridin-2-yl-ethyl)-propionamide;
3-[3-Bromo-5-(6-carbamimidoyl-1H-benzoimidazol-2-yl)-4-hydroxy-phenyl]-N-(3-phenyl-propyl)-propionamide;
5 2-[4-(6-Carbamimidoyl-1H-benzoimidazol-2-yl)-3-hydroxy-phenoxy]-N-naphthalen-1-ylmethyl-acetamide;
2-(3'-Amino-5-chloro-2-hydroxy-biphenyl-3-yl)-3H-benzoimidazole-5-carboxamidine;
3-[3-Bromo-5-(6-carbamimidoyl-1H-benzoimidazol-2-yl)-4-hydroxy-phenyl]-propionic acid;
10 2-(3,5-Bis-hydroperoxy-2-hydroxy-phenyl)-3H-benzoimidazole -5-carboxamidine;
2-[4-(5-Carbamimidoyl-1H-benzoimidazol-2-yl)-3-hydroxy-phenoxy]-N-(3-chloro-benzyl)-acetamide;
15 N-Benzyl-3-[3-bromo-5-(6-carbamimidoyl-1H-benzoimidazol-2-yl)-4-hydroxy-phenyl]-propionamide;
2-(3,5-Dibromo-2,4-dihydroxy-phenyl)-3H-benzoimidazole-5-carboxamidine;
2-(2-Hydroxy-biphenyl-3-yl)-3H-benzoimidazole-5-carboxamidine;
20 2-(5-Chloro-2-hydroxy-biphenyl-3-yl)-3H-benzoimidazole-5-carboxamidine;
2-(2-Hydroxy-3-phenethyloxy-phenyl)-3H-benzoimidazole-5-carboxamidine;
25 N-(3-Bromo-benzyl)-2-[4-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-3-hydroxy-phenoxy]-acetamide;
2-{3-[1-(3-Amino-propionyl)-pyrrolidin-2-ylmethoxy]-2-hydroxy-phenyl}-3H-benzoimidazole-5-carboxamidine;
2-(5-Chloro-2-hydroxy-3-pyridin-3-yl-phenyl)-1H-
30 benzoimidazole-5-carboxamidine;
2-[3-(5-Carbamimidoyl-1H-benzoimidazol-2-yl)-2-hydroxy-phenyl]-3,4,6,7-tetrahydro-imidazo[4,5-c]pyridine-5-carboxamidine;
2-[3-(1-Aminoacetyl-pyrrolidin-2-ylmethoxy)-2-hydroxy-phenyl]-3H-benzoimidazole-5-carboxamidine; and
35 2-(2-Hydroxy-3-phenoxy-phenyl)-3H-benzoimidazole-5-carboxamidine;

2-[2-Hydroxy-3-(1-methyl-1H-benzoimidazol-2-yl)-phenyl]-
1H-benzoimidazole-5-carboxamidine;
2-[3-(1-Aminoacetyl-piperidin-3-ylmethoxy)-2-hydroxy-
phenyl]-1H-benzoimidazole-5-carboxamidine;

5 2-{3-[1-(2-Amino-3-methyl-butyryl)-pyrrolidin-2-
ylmethoxy]-2-hydroxy-phenyl}-1H-benzoimidazole-5-
carboxamidine;

2-[2-Hydroxy-3-(1-hydroxyacetyl-pyrrolidin-2-ylmethoxy)-
phenyl]-1H-benzoimidazole-5-carboxamidine;

10 2-(2-Hydroxy-5-iodo-3-methoxy-phenyl)-1H-benzoimidazole-
5-carboxamidine;

2-{3-[1-(2-Amino-3-methyl-butyryl)-pyrrolidin-2-
ylmethoxy]-2-hydroxy-phenyl}-3H-benzoimidazole-5-
carboxamidine;

15 2-(2-Hydroxy-5-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-
benzylamino}-phenyl)-3H-benzoimidazole-5-carboxamidine;
compound with methane;

2-(2-Hydroxy-5-{4-[1-(1-imino-ethyl)-piperidin-3-
ylmethoxy]-benzylamino}-phenyl)-3H-benzoimidazole-5-
carboxamidine;

20 2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-3H-benzoimidazole-
5-carboxamidine;

3-[2,6-Dibromo-4-(6-carbamimidoyl-1H-benzoimidazol-2-yl)-
3-hydroxy-phenoxy]-propionic acid;

25 3-[2,6-Dibromo-4-(6-carbamimidoyl-1H-benzoimidazol-2-yl)-
3-hydroxy-phenoxy]-propionic acid ethyl ester; and
2-[3-Bromo-2-hydroxy-5-(3-methoxy-but-3-enyl)-phenyl]-3H-
benzoimidazole-5-carboxamidine;

3-Benzyl-2-(3-chloro-2-hydroxy-phenyl)-1H-indole-5-
30 carboxamidine;

3-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-
hydroxy-phenyl]-propionic acid;

[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-
hydroxy-phenyl]-acetic acid;

35 6-Chloro-2-(3,5-dichloro-2-hydroxy-phenyl)-1H-indole-5-
carboxamidine;

3-Bromo-5-(5-carbamimidoyl-1H-indol-2-yl)-4-hydroxy-
benzamide;

2-(3,5-Dichloro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;
3-(4-Amino-benzyl)-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;
5 2-(2-Hydroxy-biphenyl-3-yl)-1H-indole-5-carboxamidine;
2-(3-Bromo-2-hydroxy-5-nitro-phenyl)-1H-indole-5-carboxamidine;
2-(5-Hydroxy-2,3-dihydro-benzo[1,4]dioxin-6-yl)-1H-indole-5-carboxamidine;
10 3-Benzyl-2-(2-hydroxy-phenyl)-1H-indole-5-carboxamidine;
3-Benzyl-2-(3,5-difluoro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;
3-Benzyl-2-(3,5-dibromo-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;
15 [3-Bromo-5-(5-carbamimidoyl-1H-indol-2-yl)-4-hydroxy-phenyl]-acetic acid;
3-Benzyl-2-(5-chloro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;
2-[3-Bromo-5-(5-carbamimidoyl-1H-indol-2-yl)-4-hydroxy-phenyl]-acetamide;
20 2-(3,5-Difluoro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;
2-(3,5-Dibromo-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;
25 2-(2-Hydroxy-5-methyl-biphenyl-3-yl)-1H-indole-5-carboxamidine;
2-(2-Hydroxy-5,4'-dimethyl-biphenyl-3-yl)-1H-indole-5-carboxamidine;
2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;
30 3-Benzyl-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;
3-Benzyl-2-(3-chloro-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;
35 3-Benzyl-2-(2-hydroxy-3,5-dimethyl-phenyl)-1H-indole-5-carboxamidine;
2-(3,5-Dibromo-2-hydroxy-phenyl)-3-methyl-1H-indole-5-carboxamidine;

2-(2-Hydroxy-5-methyl-3-thiophen-2-yl-phenyl)-1H-indole-5-carboxamidine;
2-[2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-5-carbamimidoyl-1H-indol-3-yl]-acetamide;
5 [3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-acetic acid methyl ester;
3-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-propionic acid methyl ester;
3-(3-Amino-benzyl)-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-10 1H-indole-5-carboxamidine;
2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-3-(3-nitro-benzyl)-1H-indole-5-carboxamidine;
3-(3-Amino-benzyl)-2-(2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;
15 3-Benzyl-2-(3-chloro-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;
6-Chloro-2-{5-[2-(1,1-dioxo-1-thiomorpholin-4-yl)-2-oxo-ethyl]-2-hydroxy-biphenyl-3-yl}-1H-indole-5-carboxamidine;
20 2-[5-(5-Carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-biphenyl-3-yl]-N-(2-piperidin-1-yl-ethyl)-acetamide;
6-Chloro-2-{2-hydroxy-5-[2-(2-methoxymethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-biphenyl-3-yl}-1H-indole-5-carboxamidine;
25 6-Chloro-2-{2-hydroxy-5-[2-oxo-3-(tetrahydro-furan-2-yl)-propyl]-biphenyl-3-yl}-1H-indole-5-carboxamidine;
2-[5-(5-Carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-biphenyl-3-yl]-N-(tetrahydro-furan-2-ylmethyl)-acetamide;
2-[5-(5-Carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-30 biphenyl-3-yl]-N-(3-methoxy-propyl)-acetamide;
Morpholine-4-carboxylic acid {2-[5-(5-carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-biphenyl-3-yloxy]-ethyl}-amide;
Phosphoric acid mono-{2-[3-(3-benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-ethyl} ester;
35 2-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-N-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-phenyl}-acetamide;

4-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-butyric acid;

2-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-acetamide;

5 2-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-N,N-dimethyl-acetamide;

[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-acetic acid;

3-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-pentanedioic acid bis-[(2-morpholin-4-yl-ethyl)-amide];

10 3-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-propionamide; and

2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-3-(4-nitro-benzyl)-1H-indole-5-carboxamidine;

15 or a stereoisomer or pharmaceutically acceptable salt form thereof.

or a stereoisomer or pharmaceutically acceptable salt form thereof.

20 Yet another aspect of the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I a pharmaceutically acceptable salt thereof.

25 The present invention also provides a method for treating or preventing a thromboembolic disorder; comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

30 SYNTHESES

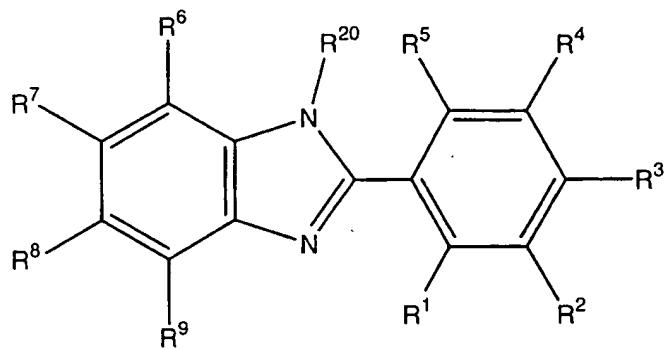
The novel compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. Described herein are some of the preferred synthetic methods for synthesizing novel compounds of the present invention. All temperatures reported herein are in degrees Celsius, unless indicated otherwise.

The novel compounds of Formula I can be prepared, using the reactions and synthetic techniques described below. It should be noted that compounds of Formula I include compounds of Formula Ia. These compounds of 5 Formula Ia represent some of the novel compounds of the present invention and can be further transformed to provide other novel compounds of the present invention.

The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for 10 the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the 15 order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

It will also be recognized that another major consideration in the planning of any synthetic route in 20 this field is the judicious choice of the protecting group used for the protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and 25 Wuts (*Protective Groups in Organic Synthesis*, Wiley and Sons, 1991).

Proton NMR's (¹H NMR) were obtained using deuterated solvents such as dimethyl sulfoxide (DMSO-d₆), deuterated chloroform (CDCl₃), or other appropriate solvents. 30 Schemes I to XXXV illustrate synthesis of precursors useful in the synthesis of compounds of Formula I, or synthesis of compounds of Formula I, having a benzimidazole nucleus, i.e., wherein "A" represents benzimidazole, and Tables 2a and 2b list them. These 35 compounds of Formula I can be represented by the following structural formula:



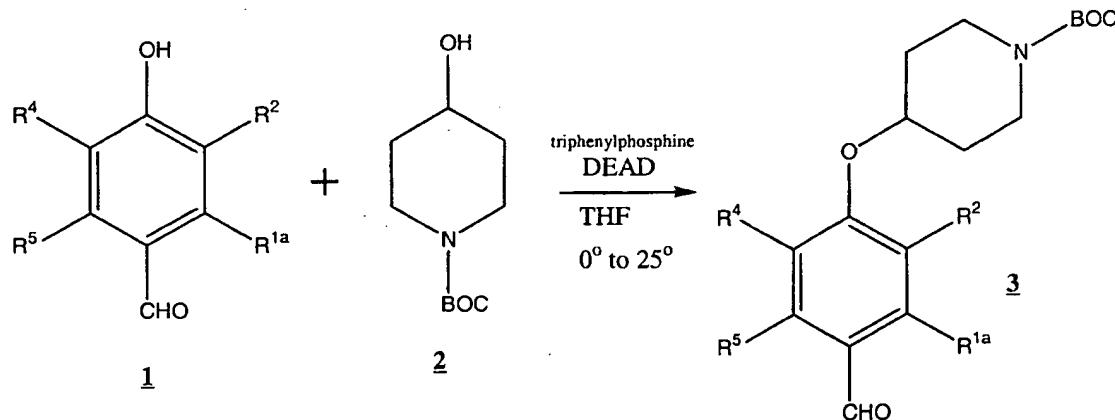
wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R²⁰ are as defined in the detailed description of the invention.

5 The aldehydes, represented by structures 3, 5, 8, 10, and 13 and the carboxylic acids represented by structures 44, 48, and 53 and 55 are useful intermediates in the synthesis of the novel compounds of Formulae I and Formula Ia. The aldehydes and carboxylic acids useful in
10 the synthesis of compounds of Formula I either are commercially available or can be prepared by the synthetic schemes outlined below.

Schemes I-IX illustrate the synthesis of aldehydes which can be used to synthesize compounds of Formula I.

15

Scheme I:

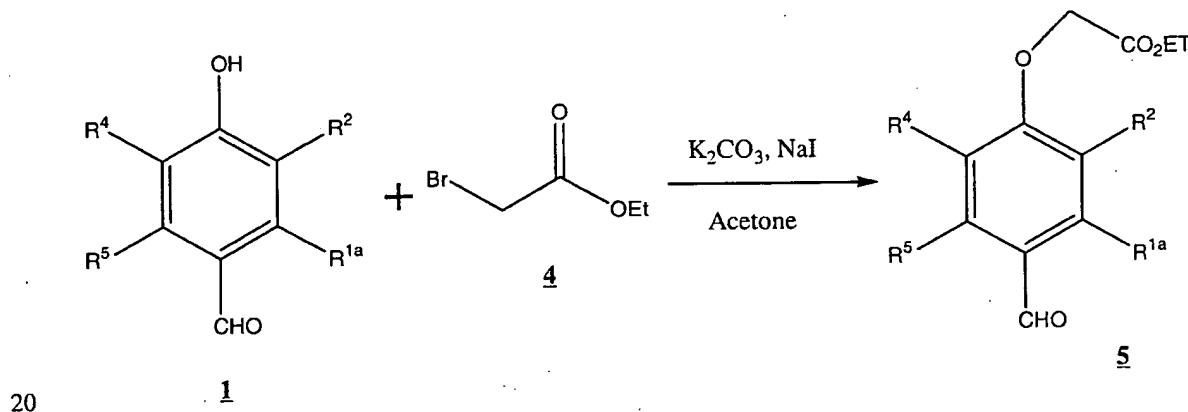


20

in which R^{1a} is H or R¹, and R², R³, and R⁵ are as defined in the detailed description.

Scheme I is a representative example of the synthesis of aldehyde 3 using the Mitsunobu reaction. The general procedure comprises mixing an appropriately substituted benzaldehyde, 1, with a Boc protected piperidinol in the presence of triphenyl phosphine in an inert solvent, such as THF, at temperatures ranging from -25° to ambient temperature, preferably 0°. To the cooled mixture is added diethyl azido dicarboxylate (DEAD) in a drop wise manner (about 0.5 to 1 mL per minute). The resulting reaction mixture is stirred at room temperature for 2 to 24 hours after which time the reaction mixture is concentrated under reduced pressure to yield a residue of the desired aldehyde, 3. Purification of the desired aldehyde can be accomplished by using methods such as chromatography, recrystallization or other methods known to one skilled in the art.

Scheme II:



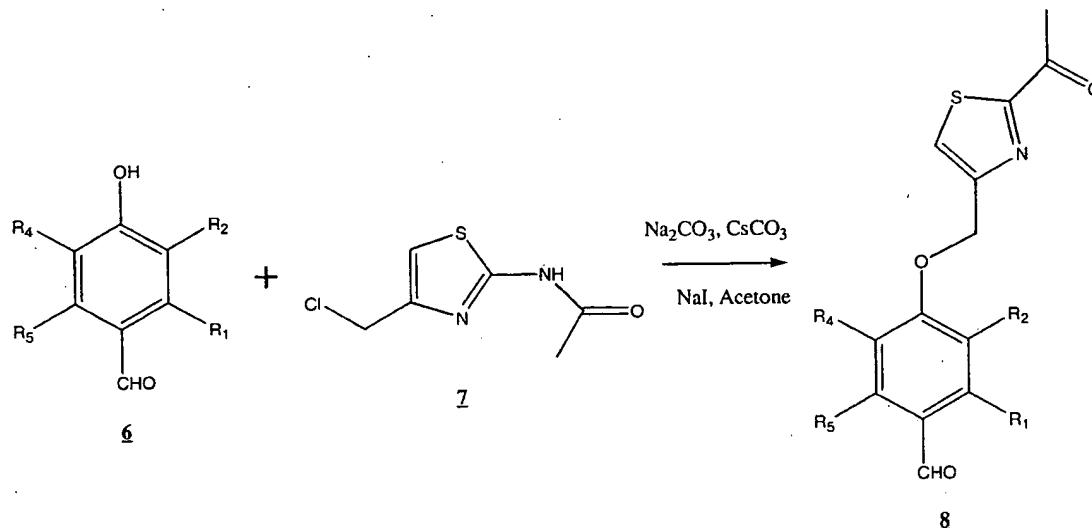
in which R^{1a} is hydrogen or the same as R¹.

Scheme II outlines the synthesis of aldehyde 5. The procedure involved forming a reaction mixture by combining an appropriate benzaldehyde 1, such as 4-hydroxy benzaldehyde, ethyl bromoacetate, 4, potassium carbonate and sodium iodide, in an inert solvent, preferably acetone. The reaction mixture is stirred at ambient temperature for 12 to 24 hours after which time

the reaction mixture is filtered through celite, and concentrated under reduced pressure to yield an oily residue. This residue can be purified by column chromatography to yield the desired aldehyde, 5.

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Scheme III:

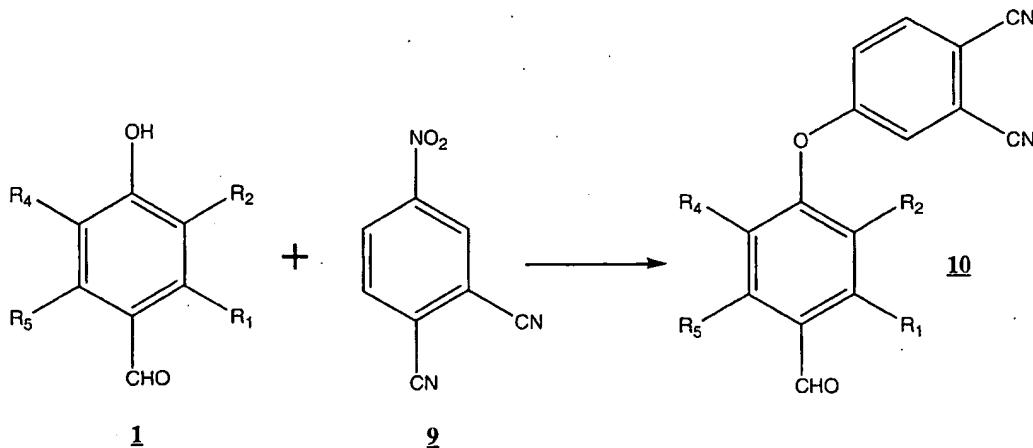


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Scheme III represents a general procedure for preparing aldehydes of formula 8. The procedure comprises mixing 4-hydroxy benzaldehyde 6, substituted thiazole 7, sodium carbonate, cesium carbonate, and sodium iodide in an inert solvent, such as acetone, to form a reaction mixture which is refluxed for eighteen hours. The reaction mixture is cooled to room temperature, filtered through celite, and the filtrate evaporated to yield a residue. The residue is dissolved in ethyl acetate and washed, in succession, with 2% aqueous sodium hydroxide, water, and brine solution. This washed organic layer is concentrated to yield the desired aldehyde 8.

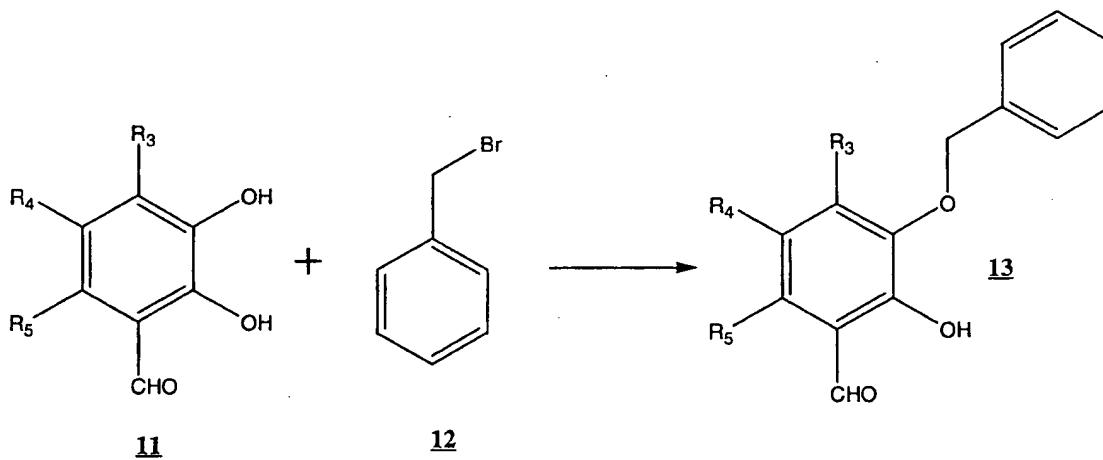
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Scheme IV:



Scheme IV depicts a method of preparing aldehyde, 10. This method comprises reacting a N,N-dimethylformamide (DMF) solution of a hydroxy benzaldehyde, 11, with sodium hydride at about 0° followed by drop wise addition (about 1 mL per minute) of a DMF solution of dicyanonitrobenzene 9. The resulting mixture is stirred from 12 to 24 hours followed by cautious pouring of the reaction mixture in ice water to yield a product. The product is collected by filtration, dried, and purified by recrystallization, e.g., from ethyl acetate, to yield aldehyde 10.

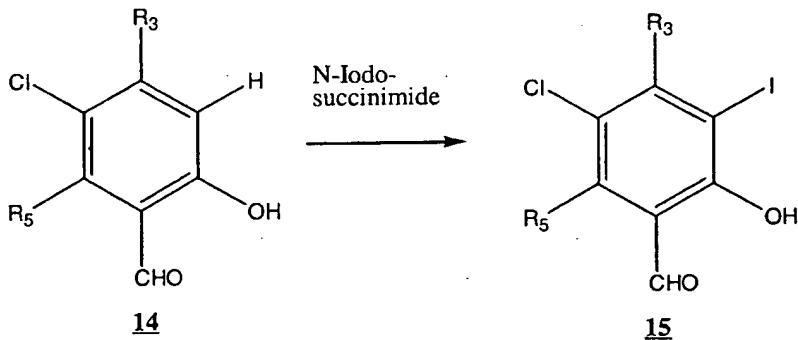
15 Scheme V



Scheme V depicts a method of preparing aldehyde 13. For example, an aldehyde of formula 11 wherein R³, R⁴ and R⁵ are hydrogen, i.e., 2,3-dihydroxybenzaldehyde (0.6g, 4.3 mmol) was added to dimethyl sulfonamide (DMSO) (10 ml) containing sodium hydride (0.25g, 10.4 mmol). After one hour a solution of benzyl bromide (0.52 ml, 4.3 mmol) in DMSO (5 ml) is added. Stirring the mixture is continued for 24 h, after which time the mixture is poured into water and extracted with chloroform (2x). The aqueous solution then was acidified with 6N hydrochloric acid to adjust the pH from 2 to about 4 and extracted with chloroform (3x). The latter organic layers were washed with 1N hydrochloric acid and filtered over silica gel to give 3-benzyloxy-2-hydroxy benzaldehyde.

¹H NMR (300 MHz, CDCl₃) δ: 11.13 (s, 1H), 9.92 (s, 1H), 7.50-6.85 (m, 8H), 5.20 (s, 2H).

20 Scheme VI

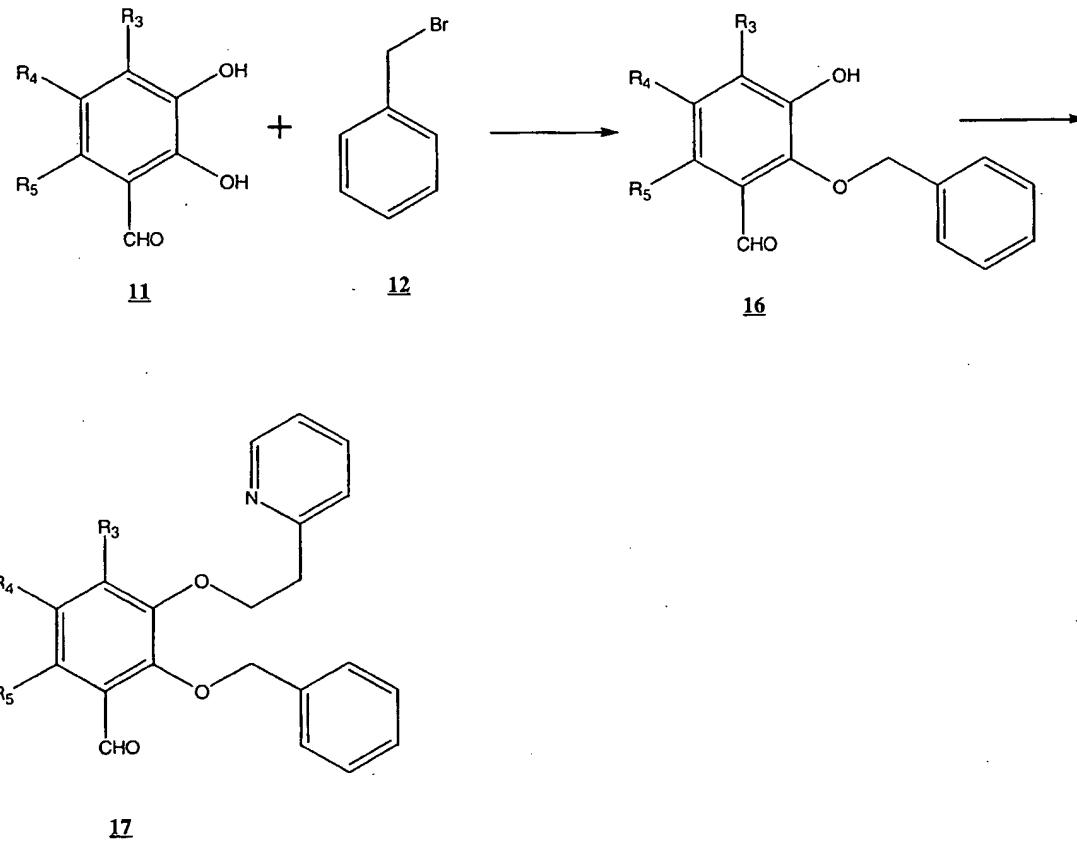


Scheme VI depicts a method for preparing aldehyde 15. For example, a mixture of an aldehyde of formula 14 wherein R³ and R⁵ are hydrogen, i.e., 5-chloro,2-hydroxy benzaldehyde (0.10 g, 0.64 mmol) and *N*-iodosuccinimide (0.16 g, 0.71 mmol) in acetic acid (2 mL) was heated to 95° C for 2 h. Another portion of *N*-iodosuccinimide (0.020 g, 0.09 mmol) was added and heating was continued for 1 h. The mixture was diluted with ethyl acetate,

washed in succession with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$, saturated NaCl , and dried (Na_2SO_4). The solvent was removed under reduced pressure, and 5-chloro-3-iodo-benzaldehyde was obtained as a yellow crystalline solid (0.17 g, 94%)

5

Scheme VII



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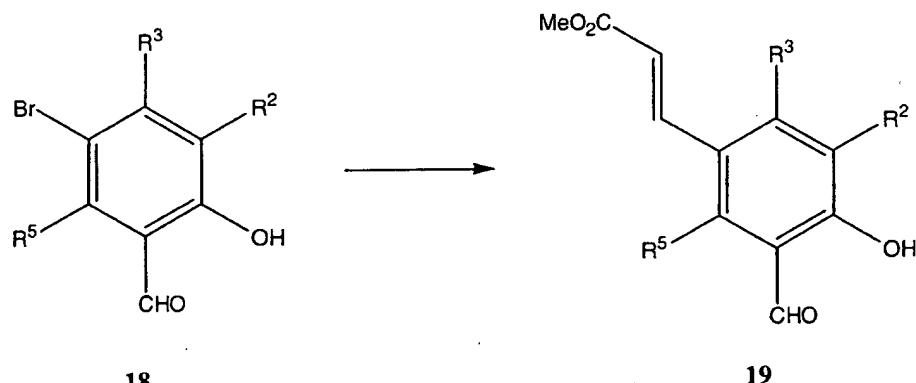
Scheme VII illustrates the synthesis of benzyl protected aldehydes 17.

For example, sodium hydride (0.52g, 21.7 mmol) is added to DMSO (20 ml) followed by an aldehyde of formula 11 wherein R³, R⁴ and R⁵ are hydrogen, i.e., 2,3-dihydroxybenzaldehyde, (2.8g, 20.2 mmol). After stirring the solution for 1 h at ambient temperature, benzyl bromide 12 (2.4 ml, 20.2 mmol) was added forming a red-brown reaction mixture which was further stirred 12 h at ambient temperature. The solution was then partitioned between ethyl acetate (200 ml) and 0.5 N hydrochloric acid (300 ml). The organic layer was separated and

MgSO4, filtered and concentrated to afford a brown oil. The brown oil is purified by flash chromatography (15% ethyl acetate / hexane) to give 3.21 g of 2-benzyloxy-3-hydroxy-benzaldehyde **16**.

5 2-benzyloxy-3-hydroxy-benzaldehyde 16 (0.30g, 1.3
mmol), triphenylphosphine (0.41g, 1.6 mmol) and 2-(2-
hydroxyethyl)pyridine (0.18 ml, 1.6 mmol) were stirred in
THF (15 ml), followed by the addition of DEAD (0.25 ml,
1.6 mmol). After stirring for 12 h, the reaction mixture
10 is partitioned between ethyl acetate (200 ml) and
saturated aqueous sodium hydrogen carbonate (200 ml).
The organic layer is separated, dried (MgSO_4), filtered
and concentrated to give a brown oil. The brown oil is
purified by flash chromatography (50% ethyl acetate/
15 hexanes) to afford 0.29 g (66%) of 2-hydroxy-3-(2-
pyridin-2-yloxy)benzaldehyde 17 as a light yellow
solid.

Scheme VIII

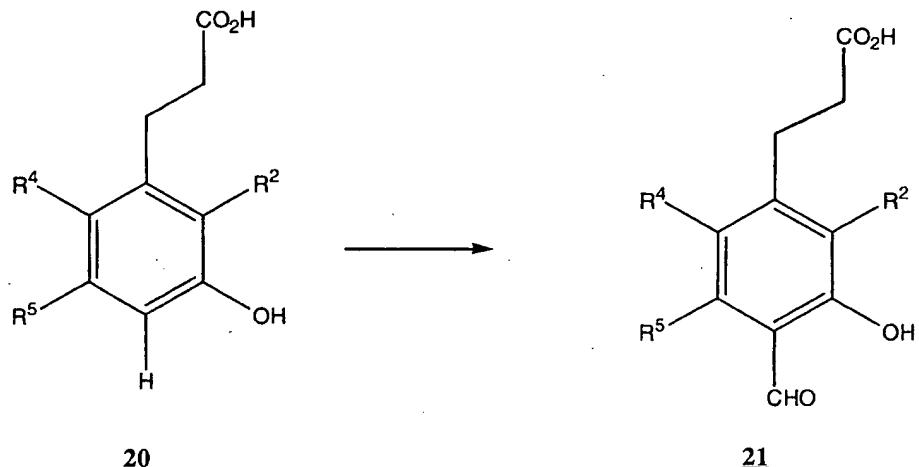


Scheme VIII outlines the Heck coupling (R. F. Heck, "Palladium Catalyzed Reactions of Organic Halides with Olefins," Accounts Chem. Res. 12, 146 (1979)) used to prepare aldehydes **19**. The bromo-benzaldehyde **18** is typically combined with the methyl acrylate (1.5 eq.), triphenyl phosphine (0.33 eq.), palladium acetate (0.15 eq.) and triethylamine (2 eq.) in benzene and the mixture refluxed for 12-18 h. After cooling the mixture is

diluted with 0.05N HCl and extracted with ethyl acetate. The organic extracts are washed with water, then brine and dried ($MgSO_4$). Filtration followed by purification over silica gel affords the desired aldehyde **19**.

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Scheme IX

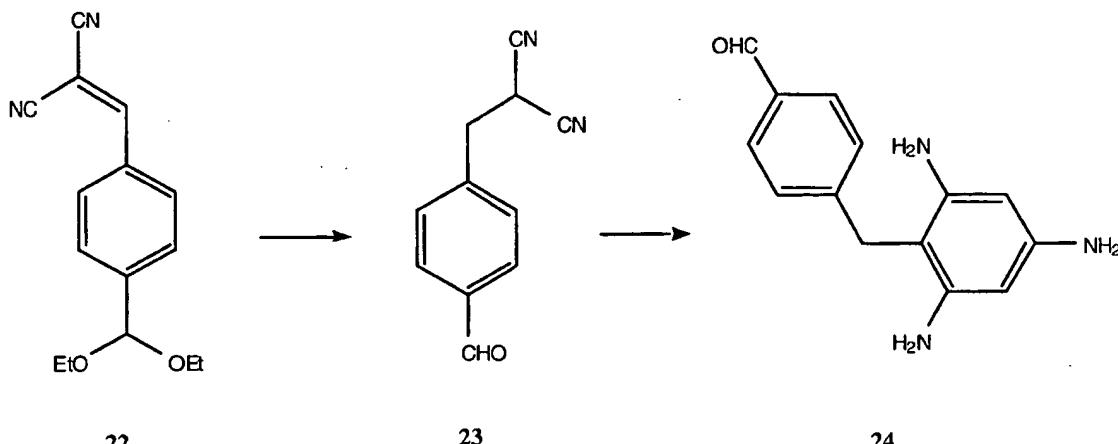
**20****21**

Scheme IX illustrates the preparation of aldehydes **21**. For example, a compound of formula **20** wherein R³, R⁴ and R⁵ are hydrogen, i.e., 3-(3-hydroxyphenyl)propionic acid, (3.0 g, 0.018 mol, Aldrich Chemical Comp, Cat 1279), NaOH (6 g, 0.15 mol), water (40 mL), and chloroform (40 ml) were combined and heated at 70°C for 12 h in a 100 ml round bottom flask. The solution is acidified to pH 4, extracted with EtOAc (2x30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 3-(4-formyl-3-hydroxy phenyl)propionic acid which was used without further purification.

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Scheme IXa



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Compound **22** was prepared by combining terephthaldehyde monodiethylacetal (Acros Chemical Comp. Cat #24069-1000, 5.0 g, 0.02 mol), malononitrile (1.32 g, 0.02 mol), EtOH (30 mL), and NaOEt (2.72 g, 0.04 mol).

10 The mixture was stirred at ambient temperature for 12 h, water (50 mL) was added, and the mixture was extracted with Et₂O (2x 50 mL). The organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure to give **22** in a 88% yield (4.5 g, 0.017 mol).

15 ¹HNMR (300 MHz, DMSO) δ: 7.95 (d, 2H), 7.75 (s, 1 H), 7.65 (d, 2 H), 7.26 (d, 1 H), 5.51 (s, 1H), 3.6 (t, 2H), 1.21 (t, 3H).

MS (CI) Calc for C₁₅H₁₆N₂O₂: 256.12, Found: M+ 257.1.

In a 100 mL round bottom flask **22** (4.5 g, 0.017 mol) and EtOH (50 mL) were combined and the mixture cooled to 0° C. NaBH₄ (1 g) was added in increments and the mixture was stirred at 0°C for 30 min. 1N HCl (50 mL) was added, the mixture was extracted with Et₂O (2x 50 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to give 4.4 g, 99% of **23**. ¹HNMR (300 MHz, DMSO) δ 10.05 (s, 1H), 7.96 (d, 2H), 7.58 (d, 2 H), 7.35 (s, 1 H), 3.45 (d, 1H).

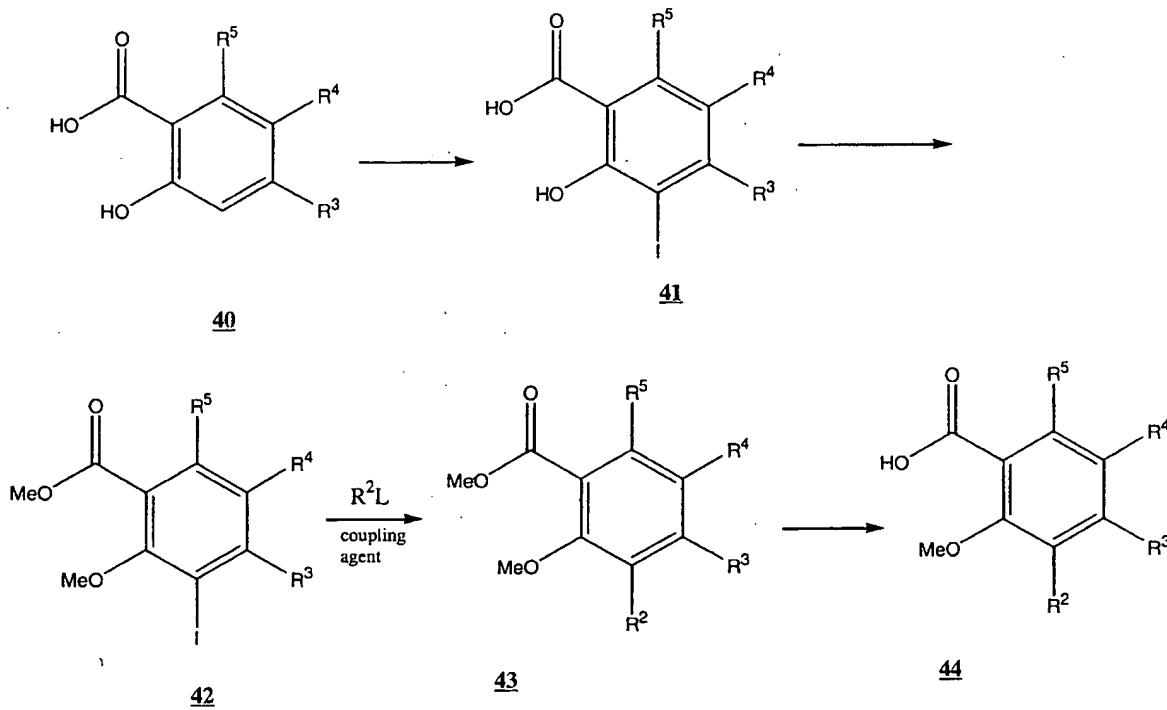
In a 100 mL round bottom flask under an atmosphere of nitrogen was placed 50 mL of EtOH. Sodium (0.28 g,

0.012 mol) was added slowly and the mixture was stirred at 0° C for 30 minutes. Guanidine hydrochloride (1.16 g, 0.012 mol) was added, the mixture was stirred at ambient temperature for an additional 30 minutes and 23 (2.0 g, 0.011) was added in one portion. The mixture was refluxed for 4 h, cooled to ambient temperature, and concentrated under reduced pressure, and the residue was triturated with Et₂O forming a precipitate. The precipitate was isolated and dried under vacuum for 12-18 h to give 24 in a 47% yield (1.2 g, 0.005 mol).

¹H NMR (300 MHz, DMSO) δ: 9.98 (s, 1 H), 7.80 (d, 2 H), 7.37 (d, 2 H), 7.24 (s, 1 H), 7.18 (br s, 6 H).

The following Schemes X-XIII illustrate the synthesis of carboxylic acids which can be used to synthesize compounds of Formula I

Scheme X:



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Scheme X shows a representative example of the synthesis of carboxylic acid 44.

For example, a mixture of a compound of formula 40 wherein R³ and R⁴ are hydrogen and R⁵ is chloro, i.e., 5-chloro-2-hydroxy benzoic acid, (5.0 g, 29 mmol) and N-iodosuccinimide (7.17 g, 32 mmol) in acetic acid (30 mL) was heated to 95° C for 2 h. Additional N-iodosuccinimide (0.70 g, 3.1 mmol) was added and heating was continued for 1 h. The mixture was cooled and poured over ice. The precipitate was isolated by filtration and the crude material was purified by recrystallization from methanol/water. The solid was isolated by filtration, rinsed with water and dried. 5-Chloro-2-hydroxy-3-iodo-benzoic acid 41 was obtained as a tan crystalline solid (6.14 g, 71 % yield).

¹H-NMR (DMSO-d₆) δ ppm: 12.0 (brs), 8.1 (s, 2H), 7.8 (s, 1H).

A solution of 5-Chloro-2-hydroxy-3-iodo-benzoic acid 41 in DMF (40 mL) was treated with K₂CO₃, (5.70 g, 41 mmol) and then stirred for 15 min. The mixture was chilled to 0° C under nitrogen and iodomethane (2.82 mL, 45 mmol) was added. This heterogeneous mixture was stirred for 18 h at 20° C. Additional K₂CO₃, (0.57 g, 4.1 mmol) and iodomethane (0.28 mL, 4.5 mmol) were added. After 6h, the mixture was diluted with ether, washed with saturated NaHCO₃, NaCl, and dried (Na₂SO₄). The solvent was removed under reduced pressure to give 5-Chloro-3-iodo-2-methoxybenzoic acid methyl ester 42 as a light purple crystalline solid (6.21 g, 93% yield).

¹H-NMR (DMSO-d₆) δ ppm: 8.15 (s, 1H), 7.75 (s, 1H), 3.85 (s, 3H), 3.75 (s, 3H).

To a solution of methyl,5-chloro-3-iodo-2-methoxybenzoic acid methyl ester (0.80 g, 2.5 mmol) and tetrakis (triphenylphosphine)palladium(0) (0.085 g, 0.074 mmol) in toluene (12 mL) was added 3-nitrobenzene-boronic acid (0.45 g, 2.7 mmol) dissolved in 1 mL of ethanol. Aqueous 2 N K₂CO₃, (2.7 mL, 5.4 mmol) was added and the mixture was heated to reflux for 18 h. The mixture was diluted with ether, washed with 3:1 saturated NaHCO₃/conc.

ammonium hydroxide, 0.1 M EDTA, saturated NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude material was purified by silica gel chromatography employing a gradient elution of 60 to 75 % CH₂Cl₂/hexane. 5-Chloro-2-methoxy-3'-nitro-biphenyl-3-carboxylic acid methyl ester **43** was obtained as an amber waxy solid (0.59 g, 75% yield).

¹H-NMR (DMSO-d₆) δ ppm: 8.4 (s, 1H), 8.3 (d, 1H), 8.1 (d, 1H), 7.7 (m, 3H), 3.8 (s, 3H), 3.4 (s, 3H).

5-Chloro-2-methoxy-3'-nitro-biphenyl-3-carboxylic acid methyl ester **43** (0.59 g, 1.8 mmol) is dissolved in THF (1.8 mL) and treated with a solution of 2 N methanolic KOH (1.8 mL, 3.7 mmol). After 16 h, the solvent is removed under reduced pressure, followed by dilution with 5 mL of 1 M HCl and 10 mL of ice cold water. The resulting precipitate is isolated by filtration, rinsed with water and dried yielding 5-Chloro-2-methoxy-3'-nitro-biphenyl-3-carboxylic acid **44** as a tan powder (0.53 g, 95 % yield).

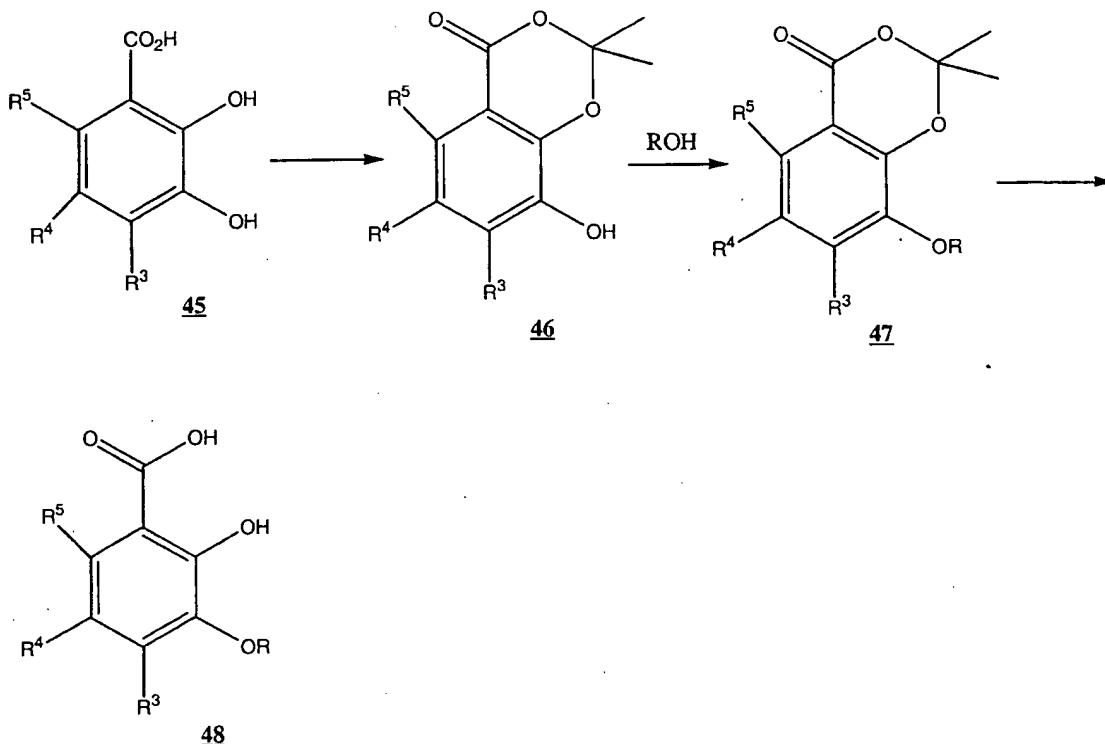
¹H-NMR (DMSO-d₆) δ ppm: 8.37 (s, 1H), 8.28 (d, 1H, J = 8.0 Hz), 8.02 (d, 1H, J = 7.6 Hz), 7.75 (m, 3H), 3.45 (s, 3H).

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Scheme XI:



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Scheme XI shows a method incorporating a Mitsonobu reaction for the synthesis of carboxylic acid **48**.

For example a compound of formula **46** wherein R^3 , R^4 and R^5 are hydrogen, i.e., 8-hydroxy-2,2-dimethylbenzo-1,3-dioxin-4-one, was prepared by the procedure of Danishefsky, S. J.; and Dushin, R. G. *J. Am. Chem. Soc.* 1992, 114, 655-659.

^1H NMR (300 MHz, CDCl_3) δ : 7.82 (d, 1H), 7.20 (d, 1H), 7.05 (t, 1H), 5.49 (s, 1H), 1.78 (s, 6H).

A solution of 8-hydroxy-2,2-dimethylbenzo-1,3-dioxin-4-one **46** (1.34 g, 6.88 mmol) and 3-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.27 g, 6.85 mmol) in THF (35 mL) under N_2 was cooled to 0°C. Triphenylphosphine (1.80g, 6.86 mmol) was added to the solution followed by addition of diethylazodicarboxylate (1.1 mL, 6.9 mmol) over 5 min. After 30 min, the reaction mixture was warmed to room

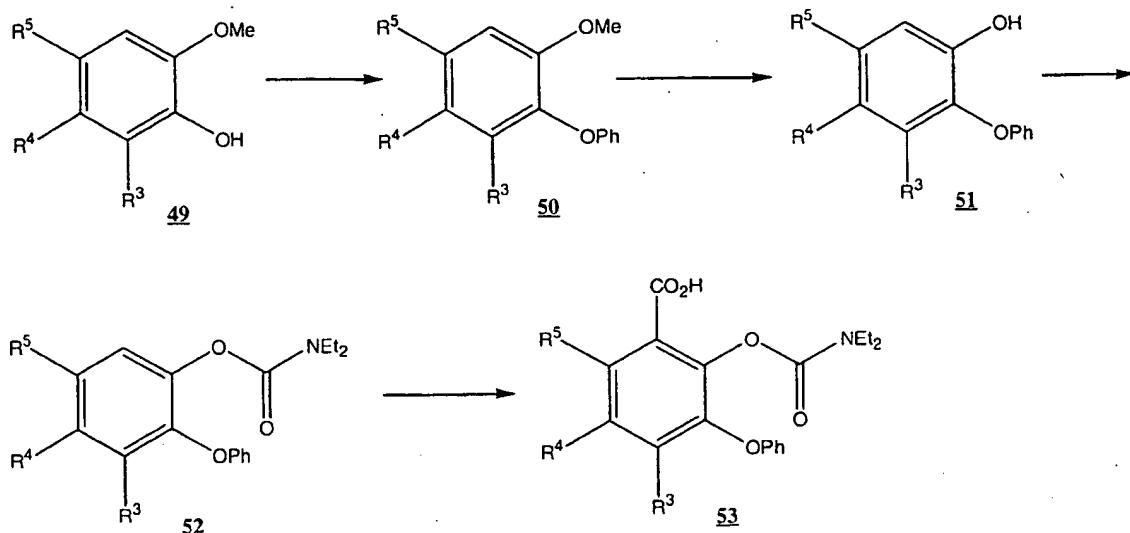
temperature and stirred for 6 h. Partial evaporation gave a concentrated crude material which was directly loaded onto a flash chromatography column (non-linear gradient 0-20-35% EtOAc in hexanes) to give 1.62 g
5 (65%) of tert-butyl 2-(2,2-dimethyl-4-oxo-4,4-benzo[1,3]dioxin-8-yloxyethyl)pyrrolidine-1-carboxylate
47 as an oil.

¹H NMR (300 MHz, DMSO-*d*₆) δ: 7.47 (m, 2H), 7.12 (t, 1H),
10 5.02 (br s, 1H), 3.7-3.2 (br m), 2.09 (br m, 2H), 1.70
(s, 6H), 1.40 (d, 9H).

tert-butyl 2-(2,2-dimethyl-4-oxo-4,4-benzo[1,3]dioxin-8-yloxyethyl) pyrrolidine-1-carboxylate
15 47 (1.65 g, 4.54 mmol) was dissolved in DMSO (9.5 mL) and then 49% aqueous KOH (1.5 mL) was added to the solution to form a basic reaction mixture. This basic reaction mixture was heated at 60°C for 40 min. After cooling to room temperature and addition of 0.5 M aqueous KHSO₄ (100 mL) gave an acidic suspension. The suspension was extracted with ether (4 x 250 mL) and the combined extracts were washed with brine (2 x 50 mL) and dried (Na₂SO₄). Evaporation of the ether gave 1.26 g (93%) of 3-(1-tert-butoxycarbonyl pyrrolidin-2-ylmethoxy)-2-hydroxy benzoic acid 48 as a brown solid.

¹H NMR (300 MHz, DMSO-*d*₆) δ: 7.41 (d, 1H), 7.25 (d, 2H),
25 6.81 (t, 1H), 4.95 (br s, 1H), 3.6-3.2 (br m), 2.05 (br m, 2H), 1.40 (s, 9H).

Scheme XII:



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Scheme XII illustrates a method for the synthesis of carboxylic acid 53.

For example a compound of formula 50 wherein R³, R⁴ and R⁵ are hydrogen, i.e., 1-methoxy-2-phenoxy benzene, was made according to the procedure in Organic Syntheses Collective Volume 3, p 566-568.

MS (chemical ionization) m/z calcd for [M + 1] 201.08, found 201.

^1H NMR (300 MHz DMSO-d₆) δ : 7.30 (t, 2H), 7.21 (m, 2H), 7.00 (m, 3H), 6.78 (d, 2H), 3.72 (s, 3H).

1-methoxy-2-phenoxy benzene 50 (0.99 g, 4.9 mmol) was dissolved in CH₂Cl₂ under a N₂ atmosphere and cooled to 0° C. A 1.0 M solution of boron tribromide in CH₂Cl₂ (7.0 mL, 7.0 mmol) was added over 5 min. The resulting reaction mixture was stirred at 0° C for 1 h and then co-evaporated with CH₃OH (4 x 30 mL) to give 0.95 g of 2-phenoxyphenyl 51.

MS (chemical ionization) m/z calcd for [M + 1] 187.07, found 187.

^1H NMR (300 MHz, CDCl₃) δ : 7.40 (t, 2H), 7.35-6.95 (m, 5H), 6.90 (m, 2H).

2-Phenoxy phenyl 51 (0.95 g, 5.1 mmol) was dissolved in pyridine under a N₂ atmosphere. Diethyl carbamyl chloride (0.65 mL, 5.1 mmol) was added to solution over 5 min after which the solution is heated at reflux for 5 h.

5 The pyridine is removed by rotary evaporation and the crude product dissolved in ether. The ether solution was washed with 0.5 M aqueous KHSO₄, followed by brine, and dried (Na₂SO₄) to give 0.60 g of crude 2-phenoxyphenyl diethyl carbonate 52. Flash chromatography (10% EtOAc in hexanes) further purified the product.

10 MS (chemical ionization) *m/z* calcd for [M + 1] 286.14, found 286.

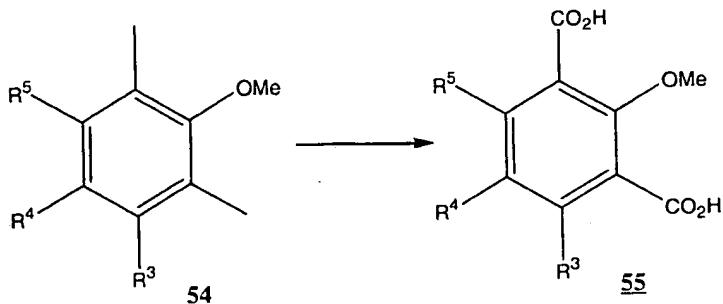
¹H NMR (300 MHz, DMSO-*d*6) δ: 7.25 (m, 5H), 7.09 (m, 2H), 6.80 (m, 2H), 3.5-3.0 (m), 0.9 (p, 6H).

15 2-phenoxyphenyl diethyl carbonate 52 (0.264 g, 0.926 mmol) was dissolved in anhydrous THF under a N₂ atmosphere using oven dried glassware. The solution was cooled to -78° C with a dry ice/acetone bath. A 1.7 M solution of *tert*-butyl lithium in pentane (0.62 mL, 1.0 mmol) was added over 4 min. After 40 min at -78° C, the atmosphere was changed to CO₂ using a balloon and kept at -78° C for 4 hr. The reaction vessel was warmed to 0° C followed by quenching with 10% aqueous NH₄Cl. The product was extracted with ether (3 x 50 mL), washed with brine (2 x 20 mL), and dried (Na₂SO₄). Rotary evaporation of ether gave 0.293 g of 2-diethyl carbamoyloxy-3-phenoxy benzoic acid 53.

20 MS (bioion) *m/z* calcd for [M + 1] 330.13, found 329.3.

25 ¹H NMR (300 MHz, DMSO-*d*6) δ: 7.59 (m, 1H), 7.20 (m, 4H), 6.98 (t, 1H), 6.81 (d, 2H), 3.08 (m, 4H), 0.8 (p, 6H).

Scheme XIII :



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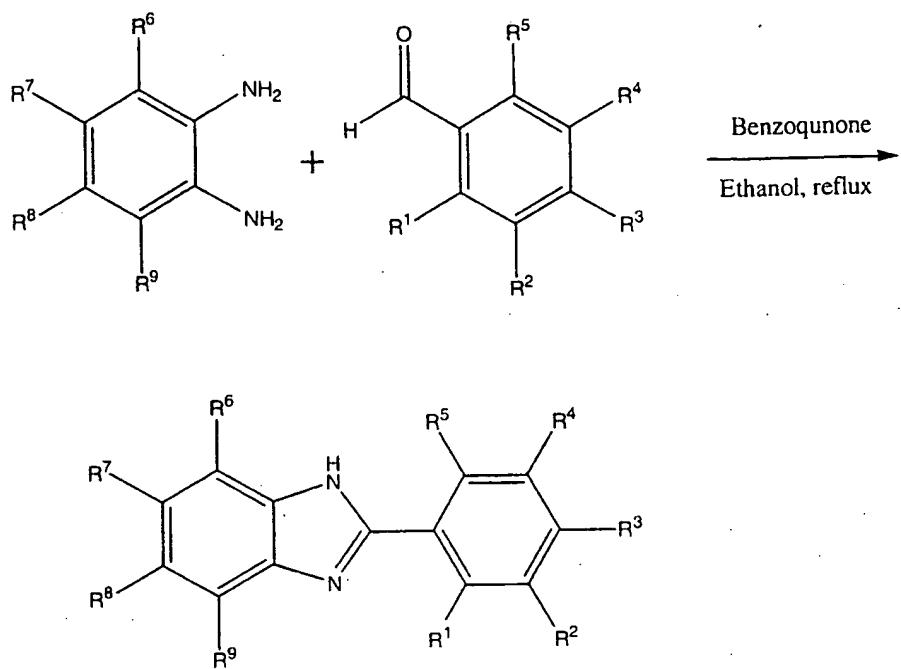
Scheme XIII illustrates the synthesis of a diacid used to make compounds of carboxylic acid 55.

For example to a 500 mL round bottom flask charged with 170mL of water and compound of formula 54, wherein
 10 R³, R⁴ and R⁵ are hydrogen, i.e., 2-methoxy-1,3-dimethylbenzene, (5 g, 36.7 mmol) was added KMnO₄ (12.2 g, 77.2 mmol). The solution was heated to a gentle reflux using an oil bath until the purple color had disappeared (2 hour). Another batch of KMnO₄ (12.2 g, 77.2 mmol) was
 15 added and the heating was continued until the purple color was destroyed (2-2.5 hour). The reaction mixture was cooled slightly and the precipitated oxides of manganese were filtered through Celite. After washing the precipitates with warm water (2 x 50 mL), the filtrate was concentrated under reduced pressure to about
 20 1/3 its original volume. This concentrated filtrate was acidified to pH 2.5 and the resulting fine white precipitate was filtered and dried overnight under reduced pressure on a high vacuum pump, yielding 2-methoxy isophthalic acid 55 as a white powder (6.8 g, 94%
 25 yield).

¹H-NMR (300 MHz, DMSO-d₆) δ: 7.97 (d, 2H), 6.9 (t, 1H), 2.5 (s, 3H).

The following schemes (XX to XXI) generally can be
 30 used to prepare compounds of Formula I having a benzimidazole nucleus.

Scheme XX



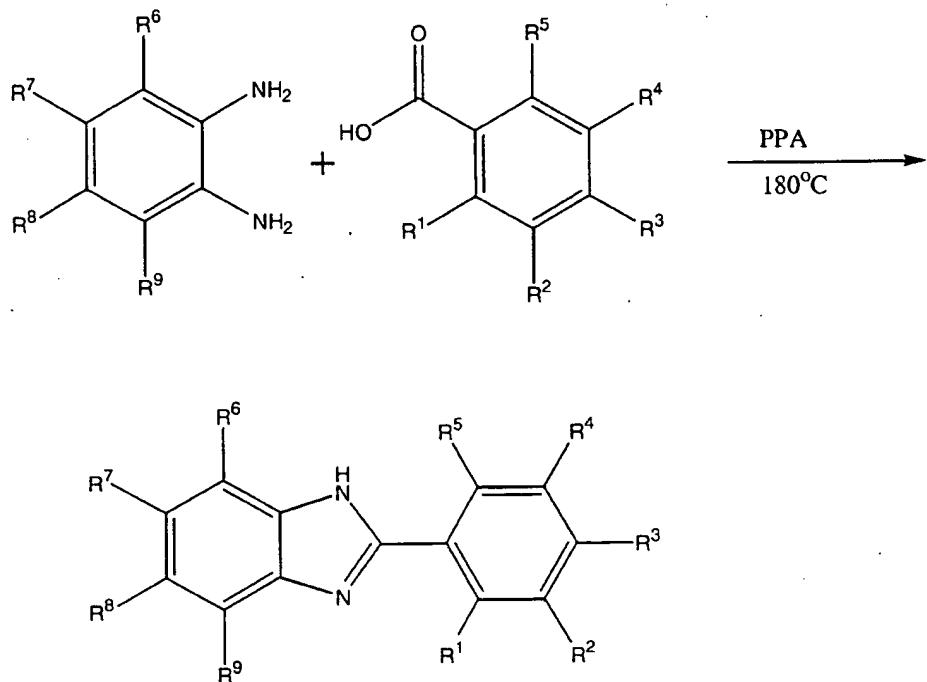
Formula Ia

5 Scheme XX outlines general procedures (Method A) for the synthesis of compounds of Formula Ia. Scheme XX requires refluxing a mixture of diaminobenzimidine monohydrochloride with an aldehyde in the presence of an oxidizing agent (e.g., benzoquinone, sodium 10 metabisulfite, and the like) in ethanol for about 12 hours. The mixture is then cooled to room temperature and poured into acetonitrile. This results in the generation of the desired product of Formula Ia which is further washed with fresh acetonitrile and dried.

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Scheme XXI



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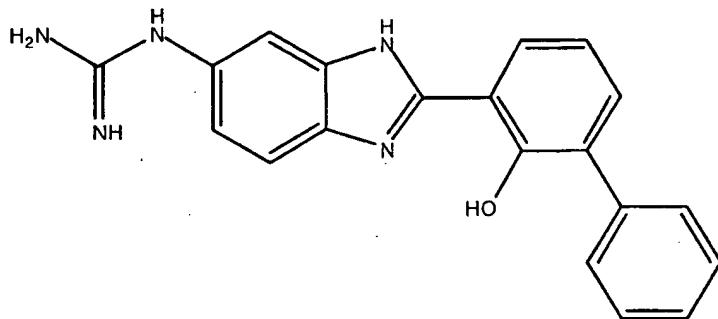
Formula I

The above Scheme XXI (Method B) can also be used to make compounds of Formula Ia. An appropriate carboxylic acid, is heated at 180°C with the hydrochloride salt of diamino benzene derivative in poly phosphoric acid (PPA) under a nitrogen atmosphere (until the carboxylic acid had reacted completely). This reaction mixture is cooled to room temperature and diluted with water (or dilute HCl) to yield a suspension. The suspension is isolated, and washed with cold water and dried to yield a compound of Formula Ia in the above scheme.

If Scheme XX or XXI utilizes appropriately protected acids or aldehydes, the final products depicted in Table 20 2 were realized by standard deprotection techniques known to one skilled in the art of organic synthesis (See Greene, 'Protecting groups in Organic Synthesis'). Thus, for example, BOC groups were removed using HCl or TFA. In the case of an aldehyde, which has a benzyl protecting

group at R², after the Method A reaction of this aldehyde with 3,4-diaminobenzamidine, the crude dark purple solid is isolated and then subjected to hydrogenation conditions in ethanol with Pd (10% on activated carbon).
5 After 2 h, the Pd is filtered and the filtrate is concentrated to ~20 ml and added to ether with vigorous stirring. After filtering and drying the product is isolated, represented by Example 172 in Table 2.

A variation of the above scheme XXI is used to make
10 Examples 100 and 200 shown below:

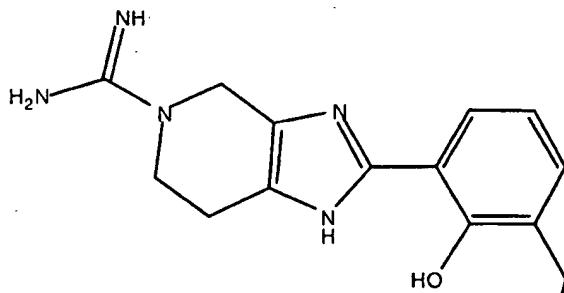


Example 100, Table

2.

15 The procedure is the same as Scheme XXI, except that 4-guanidino,1,2-diaminobenzene is used instead of 3,4-diaminobenzamidine.

Example 200 uses the acid from Scheme XIII which is reacted with 3,4,-diaminopyridine in the presence of
20 polyphosphoric acid (Method B, Scheme XXI). The resultant compound is then reduced and appropriately substituted to yield Example 200.



Example 200

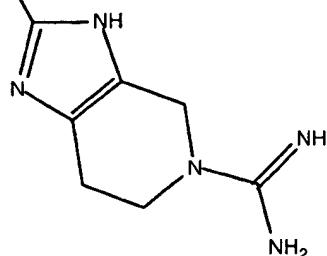
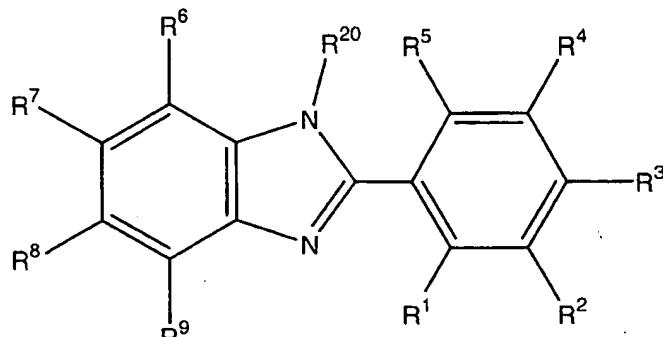


Table 2 lists examples of compounds of Formula I (and Ia) prepared by the above synthetic schemes XX and 5 XXI, methods A and B respectively.

Compounds of Formula I wherein R' is an amidino group ($\text{C}(\text{=NH})\text{NH}_2$) can also be prepared by treating compounds of Formula I wherein $\text{R}' = \text{CN}$ with NH_2OH followed by Zn in acetic acid:

Table 2: Lists some of the benzimidazole compounds represented by Formula I.



5

wherein R⁶, R⁸, R⁹ and R²⁰ represent hydrogen; and R⁷ represents amidino (or guanidino in the case of Example 100).

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁵
100	OH	Ph	H	H	H
101	OH	I	H	Cl	H
102	OH	CO ₂ H	H	H	H
103	OH	OCH ₂ Ph	H	H	H
104	OH	OCH ₂ CO ₂ H	H	H	H
105	OH	OH	H	H	H
106	OH	F	H	H	H
107	OH	OEt	H	H	H
108	OH	I	H	I	H
109	OH	Cl	H	Cl	H
110	OH	Ph	H	H	H
111	OH	Ph	H	Cl	H
112	OH	3-yl-pyridyl	H	Cl	H
113	OH	o-tolyl	H	Cl	H
114	OH	p-tolyl	H	Cl	H
115	OH	H	H	Cl	H
116	OH	OPh	H	H	H
117	OH	Pyrrolidin-2-ylmethoxy	H	H	H
118	OH	2-amino ethoxy	H	H	H

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁵
119	OH	1-H- Imidazo[4,5- -c]pyridin- 2-yl	H	H	H
120	OH	4-1H- Benzoimidaz ol-2-yl	H	H	H
121	OH	1-Methyl- 1H- benzoimidaz ol-2-yl	H	H	H
122	OH	Benzothiazo 1-2-yl	H	H	H
123	OH	4-Hydroxy- 1H- benzoimidaz ol-2-yl	H	H	H
124	OH	1H- Imidazo[4,5- -c]pyridin- 2-yl	H	H	H
125	OH	5-Fluoro- 1H- benzoimidaz ol-2-yl	H	H	H
126	OH	5-Carbamimido yl-1H- benzoimidaz ol-2-yl	H	H	H
127	OH	5-Methyl- 1H- benzoimidaz ol-2-yl	H	H	H
128	OH	H	H	CH=C HCO ₂ M e	H
129	OH	H	Me	H	H
130	OH	2-Pyridin- 2-yl-ethoxy	H	H	H
131	OH	H	H	nitr o	H
132	OH	H	OCH ₂ C O,Et	H	H
133	OH	m- nitrophenyl	H	Cl	H

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁵
134	OH	-CH ₂ CH ₂ CH ₂ CH(CH ₃) -		H	H
135	OPO ₃ H	-CH ₂ CH ₂ CH ₂ CH(CH ₃) -		H	H
136	OPO ₃ H	-CH ₂ CH ₂ CH ₂ CH(CH ₃) -		H	H
137	OH	Br	H	Me	H
138	OH	I	H	Me	H
139	OH	Pyrrolidin-3-yloxy	H	H	H
140	OH	Pyrrolidin-2-ylmethoxy	H	H	H
141	OH	H	OH	H	H
142	OH	H	3-tert-Butoxy carbonylaminopropoxy	H	H
143	OH	H	4-oxy-piperidine-1-carboxylic acid tert-butyl ester	H	H
144	OH	H	2-Benzyl oxycarbonylaminomethoxy	H	H
145	OH	H	H	OMe	H
146	OH	OH	OH	H	H
147	OH	OCH ₃	H	I	H
148	OH	NO ₂	H	NO ₂	H
150	OH	H	CH ₂ CH ₂ -COOH	H	H
151	OH	OMe	H	H	H
152	OH	OMe	H	NO ₂	H
153	OH	OMe	OMe	H	Me

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁵
154	OH	H	H	OCF ₃	H
155	OH	H	OH	H	OH
156	OH	H	H	OH	H
157	OH	H	CH ₂ CO OH	H	H
158	OH	H	OH	OH	H
159	OP(O) ₂ (OH) ₂	Me	H	H	H
160	OH	Piperidin-3-ylmethoxy	H	H	H
161	OH	Piperidin-3-yethoxy	H	H	H
162	OH	2-(3,5-Dichlorophenyl)-ethoxy	H	H	H
163	OH	4-Methoxybenzylloxy	H	H	H
164	OH	2-Cyclohexyl-ethoxy	H	H	H
165	OH	2-(4-Methoxyphenyl)-ethoxy	H	H	H
166	OH	2-(3-Chlorophenyl)-ethoxy	H	H	H
167	OH	2-(4-Chlorophenyl)-ethoxy	H	H	H
168	OH	2-(4-Fluorophenyl)-ethoxy	H	H	H
169	OH	3-Nitrobenzylloxy	H	H	H
170	OH	H	H	H	OH
171	OH	4-Fluorobenzylloxy	H	H	H
172	OH	2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-ethoxy	H	H	H
173	OH	phenethylloxy	H	H	H
174	OH	Br	H	CH ₂ COOH	H
175	OH	Cl	H	CH ₂ COOH	H

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁵
176 ²	OH	Cl	H	CH ₂ COOCH ₃	H
177 ²	OH	Cl	H	CH ₂ COOH	H
178	OH	3-nitrophenyl	H	CH ₂ CH ₂ COOCH ₃	H
179	OH	3-nitrophenyl	H	CH ₂ CH ₂ COOH	H
180	OH	Cl	H	CH ₂ COOH	H
181 ¹	OH	3-acetylaminophenyl	H	CH ₂ CH ₂ COOH	H
182	OH	3-chloro-4-fluorophenyl	H	CH ₂ CH ₂ COOH	H
183	OH	2-thienyl	H	CH ₂ CH ₂ COOH	H
184	Br	Br	H	2-tert-butoxycarbonylamino-2-carboxyethyl	H
185	OH	Br	H	2-amino-2-carboxyethyl	H
186	OH	phenyl	H	2-carboxyethyl	H
187	OH	Br	H	2-tert-Butoxycarbonylamino-3-oxo-5-phenylpentyl	H
188	OH	Br	H	2-Amino-2-phenethylcarbamoyl-ethyl	H
189 ³	OH	Br	H	CH ₂ CH ₂ COOH	H
190	OH	Cl	H	CH ₂ CH ₂ COOH	H
191 ²	OH	Cl	H	CH ₂ CH ₂ COOH	H
192 ¹	OH	Cl	H	CH ₂ COOCH ₃	H
193	OH	5-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-1-iminoethyl]-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl	H	H	H
194	OH	4-dimethylamino-phenyl)-ethoxy	H	H	H
195	OH	OCH ₃	H	H	(CH ₂) ₂ -NH ₂
196	OH	3-methoxy-phenyl-1-yl	H	methyl	H
197	OH	phenyl	H	methyl	H
198	OH	1,4-Dihydrobenzo[d][1,2]dioxin-6-yl	H	methyl	H

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁵
199	OH	4-methoxy-phenyl	H	methyl	H
200	OH	2-methoxy-phenyl	H	methyl	H
201	OH	NO ₂	H	H	H
202	OH	O-cyclopentyl	H	H	H
203	OH	O-CH ₂ -Ch(CH ₃) ₂	H	H	H
204	OH	Br	H	H	H
205	OH				
206	OH	O-ethyl	H	Br	H
207	OH	Br	H	CH ₃ COOH	H
208	OH	3-acetylamino-phenyl	H	Cl	H
209	OH	NH-CO-ethyl	H	H	H
210	OH	2-oxo-pyrrolidin-1-yl	H	H	H
211	OH	3-(2-Amino-acetylamino)-phenyl	H	Cl	H
212	OH	3-(3-amino-propionylamino)-phenyl	H	Cl	H
213	OH	Cl	H	CH ₃ COOH	H
214	OH	Br		3-[2-[(benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-ethyl]-phenyl	H
215	OH	Br	H	3-[2-(2-Morpholin-4-yl-ethylcarbamoyl)-ethyl]-phenyl	H
216	OH	Br	H	3-[2-[(Pyridin-3-ylmethyl)-carbamoyl]-ethyl]-phenyl	H
217	OH	Br	H	CH ₂ CO-NH-CH ₂ -Ph	H
218	OH	Br	H	CH ₂ CO-NH-CH ₂ -CH ₂ -Ph	H

¹ R⁷ represents C(=O)NH₂ and R⁸ represents F

² R⁸ represents F

5 ³ R⁸ represents Cl

Listed below is the proton NMR (^1H NMR) and Mass spectral data for compounds listed in Table 2.

5

Ex. 100

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 9.92 (s, 1H), 8.14 (d, 1H, $J = 7.7$ Hz), 7.72 (d, 1H, $J = 7.7$ Hz), 7.65-7.60 (m, 2H), 7.56 (s, 1H), 7.48-7.32 (m, 7H), 7.22-7.08 (m, 2H).
 MS (ES) calc. 343.1, found 343.9

10

Ex. 101

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 9.41 (s, 2H), 9.09 (s, 2H), 8.38 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.88 (d, 1H, $J = 8.3$ Hz), 7.75 (d, 1H, $J = 8.5$ Hz).

15

MS (ESI, $M^+ +1$): Calc. 412.0; Found 412.8.

Ex.: 102

$^1\text{H NMR}$ (DMSO- d_6) δ : 9.35 (s, 2H), 8.95 (s, 2H), 8.40 (d, 1H), 8.2 (s, 1H), 7.98 (d, 1H), 7.99 (t, 1H), 7.85 (d, 1H) 7.68 (d, 1H), 7.24 (d, 1H, $J = 7.4$ Hz), 6.98 (t, 1H, $J = 8.0$ Hz), 5.22 (s, 2H).
 MS (ESI, $M+1$): 296.3 (calc.); 297.0 (obs.).

25

Ex.: 103

$^1\text{H NMR}$ (DMSO- d_6) δ : 9.42 (br.s, 2H), 9.09 (br.s, 2H), 8.22 (s, 1H), 7.88 (d, 1H, $J = 8.5$ Hz), 7.80-7.75 (m, 2H), 7.49 (d, 2H, $J = 7.1$ Hz), 7.42-7.33 (m, 3H), 7.24 (d, 1H, $J = 7.4$ Hz), 6.98 (t, 1H, $J = 8.0$ Hz), 5.22 (s, 2H).
 MS: 358.14 (calc.); 358.8 (obs.).

Ex. 105

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 9.35 (s, 2H), 9.00 (s, 2H), 8.19 (s, 1H), 7.85 (d, 1H), 7.70 (d, 1H), 7.59 (d, 1H), 6.95 (d, 1H), 6.85 (t, 1H).
 MS (CI, $M^+ +1$): Calc. 268.1; Found: 268.7.

EX. 107

¹H NMR (DMSO-d₆) δ: 9.27 (br.s, 2H), 8.96 (br.s, 2H), 8.15 (s, 1H), 7.81 (d, 1H, J = 8.7 Hz), 7.68 (d, 1H, J = 10.5 Hz), 7.64 (d, 1H, J = 9.3 Hz), 7.09 (d, 1H), 6.94 (1H, t, 5 J = 7.8 Hz), 4.06 (q, 2H, 6.9 Hz), 1.33 (t, 3H, J = 6.9 Hz).

MS: 296.13 (calc.); 296.9 (obs.).

Ex. 108

10 ¹H NMR (DMSO-d₆) δ: 9.34 (br.s, 2H), 9.17 (br.s, 2H), 8.45 (s, 1H), 8.15 (m, 2H), 7.86 (d, 1H, J = 8.4 Hz), 7.73 (d, 1H, J = 8.7 Hz).

MS: 503.89 (calc.); 504.5 (obs.).

15 **Ex. 110: 2-(2-Hydroxy-biphenyl-3-yl)-3H-benzoimidazole-5-carboxamidine**

¹H-NMR (DMSO-d₆) δ ppm: 9.39 (s, 2H), 9.08 (s, 2H), 8.28-8.13 (m, 2H), 7.85 (d, 1H, J = 8.1 Hz), 7.74 (d, 1H, J = 20 8.3 Hz), 7.65-7.56 (m, 2H), 7.52-7.31 (m, 4H), 7.13 (t, 1H, J = 7.6 Hz).

MS (ESI, M⁺ + 1): Calc. 328.1; Found 328.9.

25 **Ex. 111: 2-(5-Chloro-2-hydroxy-biphenyl-3-yl)-3H-benzoimidazole-5-carboxamidine**

¹H-NMR (DMSO-d₆) δ ppm: 9.39 (br s, 2H), 9.05 (br s, 2 H), 8.33 (s, 1H), 8.23 (br s, 1H), 7.90-7.30 (m, 8H).

MS (ESI, M+1): Calc. 362.1, Found: 362.9.

30

Ex.: 112

MS (Bioion): Calc. 363.09; Found 364.0.

Ex. 113

35 ¹H-NMR (DMSO-d₆) δ ppm: 9.39 (s, 2H), 9.06 (s, 2H), 8.36 (s, 1H), 8.21 (s, 1H), 7.87 (d, 1H, J = 8.12 Hz), 7.75 (d, 1H, J = 8.2 Hz), 7.75-7.15 (m, 5H), 2.15 (s, 3H).

MS (ESI, M+1) Calc. 376.1, Found 377.0.

Ex. 114

5 $^1\text{H-NMR}$ (DMSO- d_6) δ : 14.25 (br s, 1H), 13.70 (br s, 1H),
 9.39 (s, 2H), 9.05 (s, 2H), 8.30 (br s, 2H), 7.90-7.70
 (m, 2H), 7.55-7.45 (m, 3H), 7.26 (d, 2H, $J = 7.9$ Hz),
 2.35 (s, 3H).

MS (ES) calc. 376.1, found 377.0.

10

Ex. 115

¹H-NMR (DMSO-d₆) δ ppm: 9.46 (s, 2H), 9.16 (s, 2H), 8.36 (d, 1H, J = 2.4 Hz), 8.24 (s, 1H), 7.92 (d, 1H, J = 8.5 Hz), 7.78 (d, 1H, J = 8.5 Hz), 7.51 (dd, 1H, J = 8.8, 2.4 Hz), 7.20 (d, 1H, 8.9 Hz).

MS (CI) calc. 286.7, found 287.2.

Ex. 116: 2-(2-Hydroxy-3-phenoxy-phenyl)-3H-benzimidazole-5-carboxamidine

20

¹H NMR (DMSO-d₆) δ: 9.40 (s, 2H), 9.05 (s, 2H), 8.20 (s, 1H), 8.07 (d, 1H, J = 10.5 Hz), 7.86 (d, 1H, J = 9 Hz), 7.74 (d, 1H, J = 9 Hz), 7.33 (t, 2H, J = 9 Hz), 7.23 (d, 1H, J = 9 Hz), 7.1-7.03 (m, 2H), 6.94 (d, 2H, J = 7.5 Hz).

Mass_Est (M+1) = 344.13 (galaxy); 346.2 (abs)

FIG. 117

¹H NMR (DMSO-d₆) δ: 9.98 (s, 2H), 9.22 (s, 2H), 8.27 (s, 1H), 7.92 (t, 2H, J = 6 Hz), 7.82 (d, 1H, J = 12 Hz), 7.29 (d, 1H, J = 9 Hz), 7.05 (t, 1H, J = 9 Hz), 4.38 (d, J = 12 Hz), 4.26 (t, J = 12 Hz), 4.1-3.4 (br.m), 3.4-3.1 (br.m), 2.25-1.60 (br.m, 5H).

MS (ESI): Calc.: 351.17; Obs.: 351.19.

35

Ex.: 118

5 ^1H NMR (DMSO- d_6) δ : 9.49 (s, 2H), 9.18 (s, 2H), 8.39 (s,
 2H), 8.25 (s, 1H), 7.96- 7.89 (m, 2H), 7.79 (d, 1H, J = 9
 Hz), 7.04 (t, 1H, J = 15 Hz), 4.25 (t, 2H), 4.0-3.0
 (br.m).

MS: 311.14 (calc.); 311.19 (obs.).

10 **Ex.119: 2-[3-(1H-benzoimidazol-2-yl)-2-hydroxy-phenyl]-
 1H-benzoimidazole-5-carboxamidine:**

15 ^1H NMR (d_6 - DMSO) δ : 9.55 (s, 2H), 9.2 (s, 2H), 8.7 (d,
 1H), 8.55 (d, 1H), 8.3 (s, 1H), 7.98 (d, 1H), 7.95 (t,
 1H), 7.85 (t, 1H), 7.8 (d, 1H), 7.58 (d, 1H), 7.55 (d,
 1H), 7.4 (t, 1H).

Mass ESI (M^++1): Calculated: 368.14 ; Obs.: 369.0.

Ex.: 120

20 ^1H NMR (d_6 - DMSO) δ 9.5 (s, 2H), 9.45 (s, 1H), 9.1 (d, 2H),
 8.6 (d, 1H), 8.57 (s, 1H), 8.55 (d, 1H), 8.3 (s, 1H), 8.2
 (d, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 7.4 (t, 1H).

MS: 369.13 (calc.); 370.0 (obs.).

25 **Ex.:121**

^1H NMR (d_6 -DMSO) δ : 8.35 (d, 1H); 8.15 (s, 1H); 8.07 (d,
 1H); 8.05 (d, 1H); 8.0 (t, 1H); 7.97 (t, 1H); 7.95 (d,
 1H); 7.9 (d, 1H); 7.83 (d, 1H); 7.28 (t, 2H); 4.0 (s,
 3H).

30 Mass ESI (M^++1): Calculated: 382.15; Obs.: 383.0.

Ex. 122

35 ^1H NMR (d_6 - DMSO) δ : 9.45 (s, 2H), 9.22 (s, 2H), 8.55 (d,
 1H), 8.45 (d, 1H), 8.28 (s, 1H), 8.19 (d, 1H), 8.09 (d,
 1H), 7.93 (d, 1H), 7.79 (d, 1H), 7.6 (t, 1H), 7.55 (t,
 1H), 7.45 (t, 1H).

MS: 385.10 (calc.); 385.9 (obs.).

Ex.: 123

¹H NMR (DMSO-d₆) δ: 9.4 (s, 2H), 9.05 (s, 2H), 8.22 (s, 1H), 8.2 (d, 1H), 7.80 (d, 1H), 7.78 (d, 1H), 7.38 (t, 1H), 7.20 (t, 1H), 7.05 (d, 1H), 6.75 (d, 1H).

5 MS (Bioion): Calc.: 384.4; Obs.: 384.

Ex. 124

¹H NMR (d₆-DMSO) δ: 9.4 (s, 2H), 9.05 (s, 2H), 8.55 (d, 1H), 8.52 (d, 1H), 8.49 (d, 1H), 8.4 (d, 1H), 8.25 (s, 1H), 7.95 (d, 1H), 7.75 (d, 1H), 7.50 (t, 1H), 7.3 (t, 1H).

MS: 369.13 (calc.); 370 (obs.).

Ex.: 125

15 MS: 386.13 (calc.); 387.0 (obs.).

Ex.: 126

¹H NMR (d₆- DMSO) δ: 9.5 (s, 4H), 9.2 (s, 4H), 8.57 (d, 2H), 8.3 (s, 2H), 7.95 (d, 2H), 7.29 (d, 2H), 7.4 (t, 1H), 7.29 (d, 2H).

MS: 410.16 (calc.); 411.0 (obs.).

Ex.: 127

MS: 382.15 (calc.); 383.0 (obs.).

25

Ex. 129

MS: 266.12 (calc.); 266.8 (obs.).

30

EX. 130

¹H NMR (DMSO-d₆) δ: 9.50 (br.s, 2H), 9.22 (br.s, 2H), 8.87 (d, 1H, J = 5.8 Hz), 8.58 (d, 1H, J = 7.9 Hz), 8.24 (s, 1H), 8.16 (d, 1H, J = 8.0 Hz), 7.99-7.86 (m, 3H), 7.78 (d, 1H, J = 7.4 Hz), 4.51 (t, 2H, J = 5.8 Hz), 3.61 (t, 2H, J = 5.8 Hz).

MS: 373.15 (calc.); 374.0 (obs.).

Ex. 131

¹H NMR (DMSO-d₆), 300 MHz) δ : 9.45 (s, 2H), 9.20 (s, 2H), 9.16 (d, 1H, J=2.69 Hz), 8.22 (m, 2H), 7.86 (d, 1H, J=8.52 Hz), 7.75 (d, 1H, J=8.52 Hz), 7.27 (d, 1H, J=9.17 Hz)

5 MS: 298.3 (M+1)

Ex. 132

¹H NMR (DMSO-d₆) δ : 9.44 (br. s, 2H), 9.06 (br. s, 2H), 8.18 (br. s, 2H), 7.86 (d, 1H, J=8.5 Hz), 7.75 (d, 1H, J=8.5 Hz), 6.68-6.74 (m, 2H), 4.89 (s, 2H), 4.18 (Q, 2H, J=7.1Hz), 1.22 (t, 3H, J=7.1Hz)

10 MS: Calc.: 354.13;:354.9 (obs.)

Ex. 133

¹H NMR (d₆-DMSO) δ: 9.42 (br s, 2H), 9.08 (br s, 2H), 8.53 (s, 1H), 8.44 (d, 1H), 8.30-8.05 (m, 3H), 7.95-7.75 (m, 4H).

15 MS: 407.1 (calc.); 407.9 (obs.).

Ex. 135

¹H-NMR (DMSO-d₆) δ ppm: 9.47 (s, 2H), 9.13 (s, 2H), 8.22 (s, 1H), 7.93 (s, 1H), 7.90 (d, 1H, J = 8.9 Hz), 7.80 (d, 1H, J = 8.9 Hz), 3.30-3.05 (m, 2H), 2.78 (m, 1H), 1.78 (m, 4H), 1.23 (d, 3H, J = 7.5 Hz).

20 MS (CI, M+1): 434.1 (calc.); 435.4 (obs.).

Ex.: 136

30 ¹H NMR (DMSO-d₆) δ ppm: 9.40 (s, 2H), 9.05 (s, 2H), 8.20 (s, 1H), 7.85 (s, 1H), 7.80 (d, 1H, J = 9.5 Hz), 7.70 (d, 1H, J = 9.5 Hz), 3.18-3.05 (m, 1H), 2.92-2.70 (m, 2H), 1.95 (m, 1H), 1.79-1.20 (m, 5H), 1.00 (t, 3H, J = 7.9 Hz).

35 MS (CI, M+1): 448.1 (calc.); 449.5 (obs.).

Ex. 137

¹H NMR (DMSO-d₆) δ : 9.38 (s, 2H), 9.0 (s, 2H), 8.2 (br. s, 1H), 8.03 (s, 1H), 7.86 (br. s, 1H), 7.72 (d, 1H, J=7.78 Hz), 7.60 (s, 1H), 2.35 (s, 3H).

5 MS: 345.1 (obs.).

Ex. 138

¹H NMR (DMSO-d₆) δ : 9.4 (s, 2H), 9.05 (s, 2H), 8.2 (br. s, 1H), 8.03 (br. s, 1H), 7.85 (br. s, 1H), 7.8-7.65 (m, 2H), 2.3 (s, 3H).

10 MS: 392.0 (calc.) 392.8 (obs.)

Ex. 139

15 ¹H NMR (DMSO-d₆) δ: 9.67 (br.m, 1H), 9.47 (s, 2H), 9.15 (s, 2H), 8.22 (s, 1H), 7.94-7.88 (m, 2H), 7.79 (d, 1H, J = 6 Hz), 7.30 (d, 1H, J = 9 Hz), 7.04 (t, 1H,), 5.45 (s, 1H), 3.50-3.25 (m, 4H), 2.15 (br.s, 2H).

20 MS (ES): Calc.: 337.15; Obs.: 337.7

Ex. 140

1H-NMR (DMSO-d₆) δ ppm: 9.45 (s, 2H), 9.20 (s, 2H), 8.90 (d, 1H), 8.23 (s, 1H), 8.12 (t, 1H), 7.90 (t, 2H), 7.79 (d, 1H), 7.30 (d, 1H), 7.05 (t, 1H), 4.40 (d, 1H), 4.21 (t, 1H), 4.05-3.50 (m), 3.40-3.20 (m, 2H), 3.05 (q, 1H), 2.25-1.75 (m, 5H).

25 MS (ESI): 351.17 (calc.), 352.0 (obs.)

Ex. 144

30 ¹H NMR (300 MHz, DMSO-d₆) δ : 9.51 (s, 2H), 9.18 (s, 2H), 8.22 (br.m, 2H), 7.91 (d, 1H, J=8.44 Hz), 7.80 (d, 1H, J=8.44 Hz), 7.59 (br.t, 1H), 7.36 (br.s, 5H), 6.70 (br. m, 2H), 5.13 (s, 2H), 4.08 (s, 2H), 3.3-3.7 (br.m).

MS: 446.5 (M+1)

Ex. 145

¹H-NMR (DMSO-d₆) δ ppm: 9.49 (s, 2H), 9.18 (s, 2H), 8.24 (s, 1H), 7.97-7.90 (m, 2H), 7.79 (d, 1H), 7.12 (s, 2H).
MS (ES) calc. 282.1, found 282.9.

5

Ex. 146

Mass, ESI: (M⁺+1): 284.3 (calc.); 284.9 (obs.).

Ex. 147

10 Mass, ESI: (M⁺+1): 408.2 (calc.); 408.8 (obs.).

Ex. 148

¹H NMR (DMSO-d₆) δ: 9.25 (s, 2H), 9.10 (s, 1H), 8.70 (s, 2H), 9.63 (s, 1H), 8.10 (s, 1H), 7.80 (d, 1H), 7.60 (d, 1H).
15 Mass, ESI: (M⁺+1): 342.3 (calc.); 342.9 (obs.).

Ex. 149

Mass, ESI: (M⁺+1): 347.4 (calc.); 348.0 (obs.).

20

Ex. 150

¹H NMR (DMSO-d₆) δ 9.54 (s, 2 H), 9.27 (s, 2 H), 8.28 (s, 1 H), 8.26 (d, 1 H, J = 9.7 Hz), 8.00 (d, 1 H, J = 9.0 Hz), 7.89 (d, 1 H, J = 9 Hz), 7.11 (s, 1 H), 6.98 (d, 1 H, J = 9.6 Hz), 5.0-4.0 (br s, 1 H) 2.86 (t, 2 H, J = 6.0 Hz), 2.59 (t, 2 H, J = 6.0 Hz).
25 Mass, MS (CI): 324.12 (calc.); 324.9. (obs.)

Ex. 151 2-(2-Hydroxy-3-methoxyphenyl)-3H-benzoimidazole-5-carboxamidine

30 Mass, ESI: (M⁺+1): 282.3 (calc.); 282.9 (obs.).

Ex. 152 2-(2-Hydroxy-3-methoxy-5-nitrophenyl)-3H-benzoimidazole-5-carboxamidine

35 Mass, ESI: (M⁺+1): 327.3 (calc.); 327.9 (obs.).

Ex. 153 2-(3,4-Dimethoxy-2-hydroxy-6-methylphenyl)-3H-benzoimidazole-5-carboxamidine

Mass, ESI: (M^++1): 326.4 (calc.); 326.9 (obs.).

5 Ex. 154 2-(2-Hydroxy-5-trifluoromethoxyphenyl)-3H-benzoimidazole-5-carboxamidine

Mass, ESI: (M^++1): 336.3 (calc.); 336.9 (obs.).

10 Ex. 155 2-(2,4,6-Trihydroxyphenyl)-3H-benzoimidazole-5-carboxamidine

Mass, ESI: (M^++1): 284.3 (calc.); 284.8 (obs.).

Ex. 157

15 ^1H NMR (DMSO-d₆) δ : 9.48 (s, 2 H), 9.18 (s, 2 H), 8.24 (s, 1 H), 8.23 (d, 1 H, J = 10.0 Hz), 7.95 (d, 1 H, J = 8.1 Hz), 7.82 (d, 1 H, J = 8.1 Hz), 7.10 (s, 1 H), 6.98 (d, 1 H, J = 9.6 Hz), 6.55 (s, 1 H), 5.0-4.0 (br s, 1 H, CO₂H), 3.65 (s, 2 H)

Mass, MS (CI) 310.11 (calc.); 310.9. (obs.)

20 Ex. 158 2-(2,4,5-Trihydroxyphenyl)-3H-benzoimidazole-5-carboxamidine

Mass, ESI: (M^++H): 284.3 (calc.); 284.8 (obs.).

25 Ex.: 159

1H NMR (DMSO-d₆) δ ppm: 9.37 (s, 1H), 9.11 (s, 1H), 8.18 (s, 1H), 7.86 (d, 1H, J = 7.6 Hz), 7.81 (d, 1H, J = 8.6 Hz), 7.71 (d, 1H, J = 8.3 Hz), 7.46 (d, 1H, J = 7.3 Hz), 7.24 (t, 1H, J = 7.6 Hz), 2.41 (s, 3H).

MS (ESI, M+1): 346.1 (calc.); 346.9 (obs.).

Ex. 160

1H-NMR (DMSO-D₆) δ : ppm: 9.50 (s, 2H), 9.21 (s, 2H), 9.00 (t, 1H), 8.23 (s, 1H), 8.0-7.7 (m, 3H), 7.22 (d, 2H, J = 8 Hz), 7.02 (t, 1H, 8 Hz), 4.5-3.0 (br.m), 2.8 (m, 2H), 3.38 (br.s, 1H), 2.05-1.60 (m, 4H), 1.4 (m, 1H).
MS (ESI): 365.19 (calc.); 365.9 (obs.).

Ex. 161

¹H-NMR (DMSO-d₆) δ : ppm: 9.48 (s, 1H), 9.30-9.00 (m, 3H),
 8.25 (s, 1H), 7.9 (m, 2H), 7.30 (d, 1H, J = 8 Hz), 7.23
 5 (d, 1H, J = 8 Hz), 7.02 (t, 1H, J = 8 Hz), 5.0-3.5
 (br.m), 3.3 (br.m), 2.85 (m, 1H), 2.30-2.10 (m, 1H),
 2.10-1.85 (m, 2H), 1.85-1.30 (m, 6H).
 MS (ESI): 379.20 (calc.); 379.8 (obs.)

10

Ex. 162

¹H-NMR (DMSO-d₆) δ: 9.44 (s, 2H), 9.14 (s, 2H), 8.22 (s,
 1H), 7.89-7.74 (m, 3H), 7.61 (d, 1H, J = 2.2 Hz), 7.55
 (d, 1H, J = 8.3 Hz), 7.40 (dd, 1H, J = 8.3, 2.2 Hz), 7.21
 (d, 1H, 7.8 Hz), 6.98 (t, 1H, J = 7.8 Hz), 4.27 (t, 2H, J
 15 = 6.8 Hz), 3.20 (t, 2H, J = 6.8 Hz).
 MS (ESI, M⁺ +1): Calc. 440.08; Found 441.0.

Ex. 163

20 ¹H NMR (DMSO-d₆) δ: 9.42 (s, 2H), 9.10 (s, 2H), 8.22 (s,
 1H), 7.87 (d, 1H, J = 8.5 Hz), 7.77 (m, 2H), 7.42 (d, 2H,
 J = 8.5 Hz), 7.24 (d, 1H, J = 8.0 Hz), 6.96 (m, 3H), 5.13
 (s, 2H), 3.74 (s, 3H).
 MS (ESI, M⁺ +1): Calc. 388.15; Found 389.0.

25

Ex. 164

30 ¹H NMR (DMSO-d₆) δ: 9.44 (s, 2H), 9.14 (s, 2H), 8.22 (s,
 1H), 7.88 (d, 1H, J = 8.5 Hz), 7.76 (m, 2H), 7.17 (d, 1H,
 J = 7.7 Hz), 6.98 (t, 1H, J = 7.7 Hz), 4.07 (t, 2H, J =
 6.7 Hz), 1.76-1.62 (m, 8H), 1.16 (m, 3H), 0.94 (m, 2H).
 MS (ESI, M⁺ +1): Calc. 378.21; Found 379.1.

35

Ex. 165

40 ¹H NMR (DMSO-d₆) δ: 9.45 (s, 2H), 9.15 (s, 2H), 8.23 (s,
 1H), 7.89 (d, 1H, J = 8.5 Hz), 7.81 (m, 2H), 7.28 (d, 2H,
 J = 8.6 Hz), 7.20 (d, 1H, J = 8.0 Hz), 6.99 (t, 1H, J =

8.0 Hz), 6.87 (d, 2H, J = 8.6 Hz), 4.22 (t, 2H, J = 6.9 Hz), 3.71 (s, 3H), 3.03 (t, 2H, J = 6.9 Hz).

MS (ESI, M⁺ +1): Calc. 402.17; Found 403.1.

5

Ex. 166

¹H NMR (DMSO-d₆) δ: 9.41 (s, 2H), 9.07 (s, 2H), 8.20 (s, 1H), 7.86 (d, 1H, J = 8.5 Hz), 7.75 (m, 2H), 7.49 (s, 1H), 7.33 (m, 3H), 7.20 (d, 1H, J = 8.0 Hz), 6.97 (t, 1H, J = 8.0 Hz), 4.26 (t, 2H, J = 6.7 Hz), 3.10 (t, 2H, J = 6.7 Hz).

MS (ESI, M⁺ +1): Calc. 406.14; Found 407.0.

15

Ex. 167

¹H NMR (DMSO-d₆) δ: 9.39 (s, 2H), 9.04 (s, 2H), 8.19 (s, 1H), 7.85 (d, 1H, J = 8.5 Hz), 7.74 (m, 2H), 7.38 (m, 4H), 7.18 (d, 1H, J = 8.0 Hz), 6.96 (t, 1H, J = 8.0 Hz), 4.24 (t, 2H, J = 6.7 Hz), 3.08 (t, 2H, J = 6.7 Hz).

MS (ESI, M⁺ +1): Calc. 406.14; Found 407.0.

25

Ex. 168

¹H NMR (DMSO-d₆) δ: 9.36 (s, 2H), 9.00 (s, 2H), 8.19 (s, 1H), 7.83 (d, 1H, J = 8.5 Hz), 7.40 (dd, 2H, J = 8.3, 5.9 Hz), 7.15 (m, 3H), 6.96 (t, 1H, J = 8.0 Hz), 4.23 (t, 2H, J = 6.6 Hz), 3.08 (t, 2H, J = 6.6 Hz).

MS (ESI, M⁺ +1): Calc. 390.15; Found 391.0.

Ex. 169

35

¹H NMR (DMSO-d₆) δ: 9.41 (s, 2H), 9.07 (s, 2H), 8.40 (s, 1H), 8.22 (m, 2H), 7.98-7.69 (m, 5H), 7.27 (d, 1H, J = 8.1 Hz), 7.03 (t, 1H, J = 8.1 Hz), 5.38 (s, 2H).

MS (ESI, M⁺ +1): Calc. 403.13; Found 403.9.

40

Ex. 170

¹H NMR (DMSO-d₆) δ : 9.42 (s, 2 H) 9.12 (s, 2 H) 8.25 (d, 1 H, J = 1.1) 7.95 (d, 1 H, J = 8.5) 7.76 (d, 1 H, J = 1.1) 7.27 (t, 1 H, J = 8.2) 6.63 (d, 2 H, J = 8.2).

5 MS (bioion) found: 269 Theoretical: 268.1

Ex. 171

¹H NMR (DMSO-d₆) δ: 9.42 (s, 2H), 9.09 (s, 2H), 8.21 (s, 1H), 7.87 (d, 1H, J = 8.5 Hz), 7.77 (m, 2H), 7.53 (dd, 2H, J = 7.8, 5.7 Hz), 7.22 (m, 3H), 6.98 (t, 1H, J = 8.1 Hz), 5.18 (s, 2H).

MS (ESI, M⁺ +1): Calc. 376.13; Found 376.9.

15

Ex. 172

¹H NMR (DMSO-d₆) δ: 9.53 (s, 2H), 9.25 (s, 2H), 8.24 (s, 1H), 7.93-7.80 (m, 7H), 7.28 (d, 1H, J = 8.1 Hz), 7.01 (t, 1H, J = 8.1 Hz), 4.35 (t, 2H, J = 5.7 Hz), 4.00 (t, 2H, J = 5.7 Hz).

MS (ESI, M⁺ +1): Calc. 441.14; Found 442.3.

Ex. 173

¹H-NMR (DMSO-d₆) δ: 9.39 (s, 2H), 9.05 (s, 2H), 8.20 (s, 1H), 7.87-7.72 (m, 3H), 7.38-7.16 (m, 6H), 6.97 (t, 1H, J = 9.3 Hz), 4.25 (t, 2H, J = 7.0 Hz), 3.08 (t, 2H, J = 7.0 Hz).

MS (ESI, M⁺ +1): Calc. 372.16; Found 373.0.

30 The following discussion illustrates transformation of compounds of Formula Ia, Table 2, into compounds of Formula I. Compounds of Formula I prepared by these schemes are included in Table 2a.

Compounds of Formula I in which any of R², R³, R⁴ and 35 R⁵ are amino can be prepared by reducing a corresponding compound of Formula Ia in which R², R³, R⁴ or R⁵ nitro. The reduction can be accomplished in any number of ways known to one skilled in the art. For example, a representative way of reducing the nitro group is by

catalytic hydrogenation. The catalytic hydrogenation is carried out by mixing an appropriate nitro compound of Formula I with Pearlman's catalyst in a suitable solvent (e.g., methanol). Air from the reaction vessel is removed under reduced pressure and the reaction vessel is then charged with an atmosphere of hydrogen. The resulting mixture is stirred for about 18 hours, is filtered to remove the catalyst, and is concentrated to yield the desired amine.

Compounds of Formula I in which any of R², R³, R⁴ and R⁵ are -NR¹⁰R²⁴ wherein R²⁴ is other than hydrogen, can be prepared by reductive amination of a suitable aldehyde with a corresponding compound of Formula I in which R², R³, R⁴ or R⁵ is amino. The reductive amination is carried out by stirring a mixture of the amine with the aldehyde and molecular sieves, in methanol under an atmosphere of nitrogen for about 2 hours. Sodium cyanoborohydride is then added to the reaction mixture and the resulting mixture is stirred at ambient temperature for about 15 hours. The reaction mixture is then filtered through celite and the filtrate is concentrated. The residue may be purified by chromatography.

Compounds of Formula I in which any of R², R³, R⁴ and R⁵ comprise groups containing an annular nitrogen atom may be further derivatized to an corresponding N-1-iminoethyl substituted derivative by reacting the compound with ethyl acetamide. For example, a compound of Formula I in which R⁴ is 4-(1-(1-iminoethyl)piperidin-4-yloxy)benzylamino can be prepared by reacting a corresponding compound of Formula I in which R⁴ is 4-piperidin-4-yloxybenzyl amino with ethyl acetamide hydrochloride and triethyl amine in ethanol and stirring over night under a nitrogen atmosphere. The reaction mixture is concentrated under reduced pressure and residue may be purified by column chromatography.

Compounds of Formula I in which any of R², R³, R⁴ and R⁵ are or contain a carboxy group can be prepared by hydrolyzing a corresponding compound of Formula Ia in

which R², R³, R⁴ or R⁵ is or contains a -COOR¹⁰ group. For example, a compound of Formula I in which R³ is carboxymethoxy can be prepared by hydrolyzing a compound of Formula I in which R³ is ethoxy carbonyl methoxy.

Compounds of Formula Ia in which any of R², R³, R⁴ and R⁵ are or contain a carboxy group can be derivatized to a compound of Formula I in which R², R³, R⁴ or R⁵ is or contains -CONR¹¹R¹² or -C(O)NR³³R³⁴ by reacting the acid with an appropriate amine. For example a compound of Formula I in which R³ is carboxy methoxy is converted to a compound in which R³ is 2-(1,3-dihydro isobenzofuran-5-yl)ethylcarbomyl methoxy by reacting the acid with 2-(1,3-dihydro isobenzofuran-5-yl)ethyl amine in the presence of a suitable coupling agent (e.g., N,N'-carbonyl diimidazole (CDI), PyBOP, and the like)

Compounds of Formula I in which any of R², R³, R⁴ and R⁵ are halo can be prepared by halogenating a corresponding compound of Formula I in which R², R³, R⁴ and R⁵ is hydrogen. For example, a compound of Formula I in which R² and R⁴ are bromo was prepared by reacting 4-(6-carbamimidoyl-1H-benzoimidzol-2-yl)-3-hydroxy phenoxy acetic acid (Example 203, Table 2a) (100 mg, 0.307 mmol) with N-Bromosuccinimide (55mg, 0.307 mmol) in anhydrous DMF (5 mL). The reaction mixture is allowed to stir at room temperature for 1 hr forming a deep red-orange solution, which is added dropwise to a stirring solution of anhydrous ether and the resultant red precipitate is isolated and dried under vacuum to afford 115 mg (77.4 %) of a red solid. The crude material is dissolved in a 50:50 mixture of 1N HCl/MeOH (10 mL) and purified using reverse-phase C-18 HPLC (2-50% gradient) to yield 10 mg of 2,6-dibromo-4-(6-carbamimidoyl-1H-benzoimidzol-2-yl)-3-hydroxy phenoxy acetic acid (Example 204, Table 2a) as a yellow solid.

Compounds of Formula I in which Q, Q¹, Q² and/or Q³ or L¹, L², L³ and/or L⁴ are N-R³⁷ can be prepared by reacting a corresponding compound of Formula I in which Q, Q¹, Q² and/or Q³ or L¹, L², L³ and/or L⁴ is NH with a suitable

protected amino acid. The reaction is typically carried out in the presence of a coupling agent (e.g., PyBOP, CDI, and the like). For example a compound of Formula I in which R² is 1-aminoacetyl pyrrolidin-3yloxy was prepared by coupling a PyBrOP peptide onto Example 139, Table 2 to give the product Example 208, Table 2a.

10 tert-Butoxycarbonyl amino acetic acid and 2-(2-hydroxy-3-pyrrolidin-3-yloxyphenyl)-1H-benzoimidazole-5-carboxamide Example 139 (Table 2), were suspended in DMF (1.0 mL) under a N₂ atmosphere. Diisopropylethylamine was added and the mixture was cooled in a water/ice bath at 0°C. PyBrOP was quickly added to the cold suspension. The mixture was allowed to warm to ambient temperature to form a solution. The reaction was allowed 2 h and then 15 the reaction mixture was added to EtOAc forming a precipitate. The precipitate was isolated and dissolved in 3M aqueous HCl using a vortex mixer. This solution was kept at rppm temperature for 25 minutes and then diluted with H₂O and CH₃CN. The mixture was filtered. 20 Preparatory HPLC (linear gradient, 2-35% CH₃CN in 0.01 M aqueous HCl) followed by lyophilization gave 28 mg a of Example 208, Table 2a.

Analytical HPLC, (λ = 214 nm), 99%.

25 Compounds of Formula I in which any of R², R³, R⁴ and R⁵ are or contain a NHSO₂R (R = alkyl, aryl, and the like) group can be prepared by sulfonating a corresponding compound of Formula I in which R², R³, R⁴ or R⁵ are or, contain an amino group. For example, a compound of Formula I wherein R² is methyl sulfonyl amino is prepared 30 as follows.

A mixture of 2-(3'-Amino-5-chloro-2-hydroxy-biphenyl-3-yl)-1H-benzoimidazole-5-carboxamide (0.070 g, 0.15 mmol) and THF/water (1:1, 0.5 mL) is chilled (0° C) and treated with 2 N NaOH (0.16 mL, 0.32 mmol) and methane sulfonyl chloride (0.013 mL, 0.16 mmol) in alternating portions. The mixture is kept at 0° C for 35 1 h and then treated with another portion of 2 N NaOH (0.016 mL, 0.032 mmol) and methane sulfonyl chloride

73

(0.001 mL, 0.013 mmol). After another 1 h, the solvents were reduced in volume under reduced pressure, and the crude material is purified by C18 reversed-phase HPLC (2-65 % MeCN/H₂O containing 20 mM HCl, over 50 min:). The appropriate fractions were pooled and the solvent is removed under reduced pressure. 2-(5-chloro-2-hydroxy-3'-methanesulfonylamino-biphenyl-3-yl)-1H-benzoimidazole-5-carboxamidine **74** is obtained as a tan powder (0.012 g, 16 % yield) (Example 288, Table 2a):

Compounds of Formula I in which A is 4-(5-carbamimidoyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl can be prepared by hydrogenating a corresponding 1H-imidazo[4,5-c]pyridinyl derivative to give a 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridinyl intermediate and then reacting the intermediate with 1H-pyrazole-1-carboxamide. The hydrogenation is carried out under standard conditions. For example, the hydrogenation can be effected with a suitable catalyst (e.g., PtO₂, etc.) in a suitable solvent (e.g., methanol).

The reaction with the amidine typically is carried out in the presence of base (e.g., Hunig's base, etc.) in a suitable solvent (e.g., anhydrous DMF) at 20° to 100°C and requires 12 to 24 h to complete. Compounds of Formula I can be prepared by proceeding as in Scheme XXI but substituting an appropriate diamino pyrrolidine derivative for the diamino benzene derivative.

PtO₂ (20 mg) and concentrated hydrochloric acid (5 mL) was added to a solution of 2-[2-Hydroxy-3-(1H-imidazo[4,5-c]pyridin-2-yl)-phenyl]-1H-benzoimidazole-5-carboxamidine (Example 120, Table 2) (100 mg, 0.27 mmol) in MeOH (20 mL). The mixture was hydrogenated at 50 psi in a Parr apparatus for 12-18 h. After the hydrogenation was completed, the catalyst was filtered and the filtrate was concentrated to dryness. HPLC purification (2-50% acetonitrile / 60 minutes) followed by lyophilization afforded 2-[2-Hydroxy-3-(4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-phenyl]-1H-benzoimidazole-5-

carboxamidine 75 as pale yellow powder (20 mg, 20% yield) (Example 296, Table 2a).

Hunig's base (0.042 mL, 0.24 mmol) was added to a suspension of 2-[2-Hydroxy-3-(4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-phenyl]-1H-benzoimidazole-5-carboxamidine 75 (19mg, 0.04 mmol) and 1H-pyrazole-1-carboxamidine hydrochloride (12 mg, 0.082 mmol) in anhydrous DMF and the mixture was stirred for 12-18 h at 80 °C. The mixture was poured into water (15 mL) / diethyl ether (15 mL). The aqueous layer was washed with diethyl ether (3 x 10 mL) and concentrated to dryness. HPLC purification (2-50% acetonitrile / 60 minutes) afforded 2-[3-(5-Carbamimidoyl-1H-benzoimidazol-2-yl)-2-hydroxy-phenyl]-3,4,6,7-tetrahydro-imidazo[4;5-c]pyridine-5-carboxamidine 76 as a lyophilized yellow light powder (15.5 mg, 75% yield) (Example 298, Table 2a).

Ex.: 193

20

¹H NMR (300 MHz, ¹H, DMSO-d6): δ 9.5 ppm, (s, 2H), 9.2 (s, 2H), 8.2 (s, 1H), 7.9-7.7 (m, 3H), 7.65 (bs, 2H), 7.55 (d, 2H), 7.2 (d, 1H), 7.0 (t, 1H), 4.3 (t, 2H), 3.15 (t, 2H), 3.05 (s, 6H).

25 MS (ESI) m/z = 415.8 (MH+, calc 415.2).

Ex.: 194

¹H NMR (300 MHz, ¹H, DMSO-d6): δ 9.5 ppm, (s, 2H), 30 9.3 (s, 2H), 8.1 (s, 2H), 7.8 (d, 1H), 7.6 (s, 1H), 2.3 (s, 3H).

MS (ESI) m/z = 362.6, 364.3 (MH+, calc 362.0).

35

Ex.: 195

5 ^1H NMR (300 MHz, ^1H , DMSO-d6): δ 9.5 ppm, (s, 2H),
9.2 (s, 2H), 8.3 (s, 1H), 8.1 (bs, 2H), 7.9 (d, 1H),
7.8 (d, 1H), 7.2 (d, 1H), 6.9 (d, 1H), 3.9 (s, 3H), 2.6
(m, 4H), 1.7 (t, 2H).
5 MS (ESI) m/z = 339.9 (MH+, calc 339.17).

Ex.: 196

10 ^1H NMR (300 MHz, ^1H , DMSO-d6): δ 9.4 ppm, (s, 2H),
9.0 (s, 2H), 8.2 (bs, 1H), 8.0 (s, 1H), 7.9 (m, 1H),
7.7 (d, 1H), 7.45-7.25 (m, 2H), 7.2 (d, 2H), 6.9 (d, 1H),
3.8 (s, 3H), 2.4 (s, 3H).
MS (ESI) m/z = 372.9 (MH+, calc 372.2).

15 **Ex.: 197**

10 ^1H NMR (300 MHz, ^1H , DMSO-d6): δ 9.5 ppm, (s, 2H),
9.2 (s, 2H), 8.0 (s, 2H), 7.8-7.65 (bs, 1H), 7.6 (d,
2H), 7.4 (t, 2H), 7.35-7.25 (m, 2H), 2.35 (t, 3H).
20 MS (ESI) m/z = 360.9 (MH+, calc 360.1).

Ex.: 198

10 ^1H NMR (300 MHz, ^1H , DMSO-d6): δ 9.4 ppm, (s, 2H),
9.1 (s, 2H), 8.2 (bs, 1H), 8.0 (s, 1H), 7.9 (d, 1H),
7.7 (d, 1H), 7.3 (s, 1H), 7.2 (s, 1H), 7.1 (d, 1H),
7.0 (d, 1H), 6.0 (s, 2H), 2.3 (s, 3H).
MS (ESI) m/z = 386.9 (MH+, calc 386.14).

30 **Ex.: 199**

10 ^1H NMR (300 MHz, ^1H , DMSO-d6): δ 9.4 ppm, (s, 2H),
9.1 (s, 2H), 8.2 (s, 1H), 8.0 (s, 1H), 7.8 (d, 1H), 7.7
35 (d, 1H), 7.6 (d, 2H), 7.3 (s, 1H), 7.0 (d, 2H), 3.8 (s,
3H), 2.3 (s, 3H).
MS (ESI) m/z = 372.9 (MH+, calc 372.2).

Ex.: 200

5 ^1H NMR (300 MHz, ^1H , DMSO-d6): δ 9.4 ppm, (s, 2H),
9.1 (s, 2H) 8.2 (s, 1H), 8.0 (s, 1H), 7.8 (d, 1H), 7.7
(d, 1H), 7.4 (t, 1H), 7.2 (t, 1H), 7.15-7.05 (m, 2H),
7.0 (t, 1H), 3.7 (s, 3H), 2.3 (s, 3H).
MS (ESI) m/z = 373.0 (MH+, calc 372.2).

10

Ex.: 201

15 ^1H NMR (300 MHz, ^1H , DMSO-d6): δ 9.4 ppm (s, 2H), 9.1
(s, 2H), 8.6 (d, 1H), 8.3 (s, 1H), 8.1 (d, 1H), 7.9 (d,
1H), 7.8 (d, 1H), 7.3 (t, 1H).
MS (ESI) m/z = 297.8 (MH+, calc 297.3).

Example 267 Table 2a

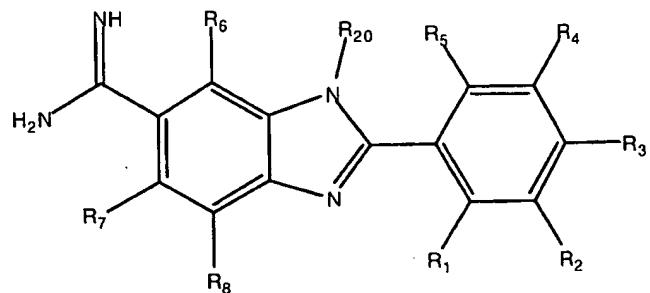
To a solution of 2-[(4-amino)-2-phenol]-3H-
benzoimidazole (0.084 g, 0.31mmol) in 4.5 ml of 2:1
DMF/DCM under nitrogen, is added 4-morpholinecarbonyl
chloride (35 uL, 0.30 mmol) followed by N,N-
diisopropylethylamine (108 uL, 0.62 mmol, 2 eq.). After
stirring for 12-18 h the solvent is removed by rotovapor
and the crude residue purified by reverse phase HPLC.
Appropriate fractions were combined and lyophilized to a
yellow solid (18 mg, 15 % yield).

Example 285 Table 2a

30 To a cold (0°C) solution of 2-(5-amino-2-hydroxy-
phenyl)-3H-benzimidazole-5-carboxamidine dihydro- chloride
(0.203 g, 0.6 mmol) in dry pyridine under nitrogen is
added methane sulfonyl chloride (93 uL, 1.2 mmol)
dropwise. After stirring the solution for 12-18 h
followed by warming it to ambient temperature the solvent
is removed and the residue is purified by reverse phase

HPLC. Appropriate fractions were lyophilized to an off white solid. (125 mg, 60% yield).

Table 2a.



5

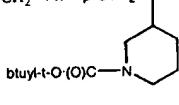
Formula I

wherein R¹ is OH; and R⁵, R⁶, R⁸, R⁹ and R²⁰ represent hydrogen.

Ex. No.	R ²	R ³	R ⁴	R ⁸
301	H	2-(Naphthale ne-2- sulfonylam ino)- ethoxy	H	H
302	H	(2,3- Dichloro- benzylcarbam oyl)-methoxy	H	H
303	H	-OCH ₂ COOH	H	H
304	Br	-OCH ₂ COOH	Br	H
305	H	(3-Chloro- benzylcarb amoyl)- methoxy	H	H
306	H	(3-bromo- benzylcarb amoyl)- methoxy	H	H
307	H	H	4-[1-(1- Imino- ethyl)- piperidin- 3- ylmethoxy]- benzylamino	H

Ex. No.	R ²	R ³	R ⁴	R ⁶
308	Pyrrolidi n-2- ylmethoxy	H	H	
309	H	H	NH ₂	H
310	H	[(Benzo[1, 3]dioxol- 5- ylmethyl)- carbamoyl] -methoxy	H	H
311	H	[(3- Chloro- benzylcarb amoyl)- methoxy]	H	H
312	1- carbamimi doy 1- piperidin -3- ylmethoxy	H	H	H
313	H	Benzylcarb amoyl- methoxy	H	H
314	H	[2-(1H- Indol-2- yl)- ethylcarba moyl]- methoxy	H	H
315	H	(3,5- Dimethoxy- benzylcarb amoyl)- methoxy	H	H
316	H	2-[2-(3,4- Dichloro- phenyl)- acetylamin o]-ethoxy	H	H
317	H	(2- Methoxy- benzylcarb amoyl)- methoxy	H	H

Ex. No.	R ²	R ³	R ⁴	R ⁵
318	H	3- Benzoylami no-propoxy	H	H
319	H	[2-(4- Hydroxy- phenyl)- ethylcarba moyl]- methoxy	H	H
320	H	3-[2-(3- Bromo- phenyl)- acetylamin o]-propoxy	H	H
321	H	3-(3- Phenyl- propionyla mino)- propoxy	H	H
322	H	2- phenylacet ylamino- ethoxy	H	H
323	H	2- Phenylmeth anesulfony lamino- ethoxy	H	H
324	H	2-(6,7- Dimethoxy- 3,4- dihydro- 1H- isoquinoli n-2-yl)-2- oxo-ethoxy	H	H
325	(2-Cyano- ethylcarb amoyl)- methoxy	H	H	H
326	H	2-(3- Phenyl- propionyla mino)- ethoxy	H	H

Ex. No.	R ²	R ³	R ⁴	R ⁶
327	H	2-Benzoylamino-ethoxy	H	H
328	H	H	3-(Piperidin-4-yloxy)-benzylamino	H
329	H	2-(3,4-Dimethoxy-phenyl)-ethylcarbamoyl]-methoxy	H	H
330	(2-Morpholin-4-yl-ethylcarbamoyl)-methoxy	H	H	H
331	2-(2-Amino-3-hydroxy-propionyl)-2,3,4,7-tetrahydron-1H-[2]pyridin-6-yl	H	H	H
332	-OCH ₂ C(O)NH-CH ₂ CH ₂ -NHC(O)CH ₃	H	H	H
333	1-(2-Amino-3-methylbutyryl)-pyrrolidin-2-ylmethoxy	H	H	H
334	H	H	NH-CH ₂ -Ph-p-OCH ₂ 	H
335	(2-p-Tolyl-ethylcarbamoyl)-methoxy	H	H	H

Ex. No.	R ²	R ³	R ⁴	R ⁸
336	5- Iminometh yl- 4,5,6,7- tetrahydr o-3H- imidazo[4 ,5- c]pyridin -2-yl	H	H	H
337	(2,3- Dimethoxy - benzylcar bamoyl)- methoxy	H	H	H
338	H	H	3-(4- Amino- cyclohexy l)- propylami no	H
339	H	[(1H- Benzimidida zol-2- ylmethyl)- carbamoyl] -methoxy	H	H
340	5-Acetyl- 4,5,6,7- tetrahydr o-3H- imidazo[4 ,5- c]pyridin -2-yl	H	H	H
341	H	-OCH ₂ COOH	Br	H
242	H	H	4-(4- Acetimido ylamino- cyclohexy loxy)- benzylami no	H
343	Br	OCH ₂ CO ₂ C ₂ H ₅	Br	H

Ex. No.	R ²	R ³	R ⁴	R ⁵
344	H	H	CH ₂ CH ₂ CO ₂ Me	H
345	H	H	4-[1-(1-Iminoethyl)-piperidin-4-yloxy]-benzylamino	H
346	1-Aminoacetyl-piperidin-3-ylmethoxy	H	H	H
347	H	(2,3-Dimethoxybenzylcarbamoyl)-methoxy	H	H
348	H	H	3-(4-Acetimidoylamino-cyclohexyloxy)-benzylamino	H
349	H	2-(2,3-Dichlorobenzoylamino)-ethoxy	H	H
350	H	naphthalen-1-ylcarbamoyl methoxy	H	H
351	H	H	4-[1-(1-Iminoethyl)-pyrrolidin-3-yloxy]-benzylamino	H
352	H	O(CH ₂) ₃ NHC(O)CH ₂ -Ph	H	H
353	Br	H	(CH ₂) ₂ C(O)NH(CH ₂) ₂ -Ph	H
354	O(CH ₂) ₂ NHCOPh	H	H	H
355	2-(3-Carbamoyl-propionylamino)-ethoxy	H	H	H

Ex. No.	R ²	R ³	R ⁴	R ⁵
356	Br	H	4-[2-(2-Pyridin-2-yl-ethylcarbamoyl)-ethyl]-benzoic acid	H
357	Br	H	(CH ₂) ₂ C(O)NH(CH ₂) ₃ -Ph	H
358	H	[(Naphthalen-1-ylmethyl)-carbamoyl]-methoxy	H	H
359	H	(3,4-Dimethoxybenzylcarbamoyl)-methoxy	H	H
360	OCH ₂ NHCH ₂ COOC(CH ₃) ₃	H	H	H
361	4-(2-Hydroxy-acetylamo)-1-methyl-butoxy	H	H	H
362	H	(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-methoxy	H	H
363	H	2-(3,4-Dichlorobenzoylamino)-ethoxy	H	H
364	H	H	4-[2-(2-Hydroxycarbonimidoyl-pyridin-3-yloxy)-ethoxy]-benzylamino	H

Ex. No.	R ²	R ³	R ⁴	R ⁸
365	H	H	4-(4-Amino-cyclohexyloxy)-benzylamino	H
366	H	H	3-(3,4-Dicyano-phenoxy)-benzylamino	H
367	H	H	(Morpholine-4-carbonyl)-amino	H
368	1-(2-Amino-3-methylbutyryl)-pyrrolidin-2-ylmethoxy	H	H	H
369	H	1-Benzoyl-piperidin-4-yloxy	H	H
371	2-(5-Oxo-4,5-dihydro-3H-pyrrol-2-ylamino)-ethoxy	H	H	H
372	5-(2-Amino-3-carboxy-propionyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl	H	H	H
373	OCH ₂ C(O)NH(CH ₂) ₂ CH(C _H) ₂	H	H	H

Ex. No.	R ²	R ³	R ⁴	R ⁵
374	2- Benzene- sulfonylamino- ethoxy	H	H	H
375	H	(9H- Fluoren-9- ylcarbamoyl)- methoxy	H	H
376	H	2-Oxo-2- (1,3,4,9- tetrahydro -b- carbolin- 2-yl)- ethoxy	H	H
377	H	1-(3- Phenyl- propionyl) - piperidin- 4-yloxy	H	H
378	1-(3- Amino- propionyl) - pyrrolidi- n-2- ylmethoxy	H	H	H
379	H	H	1-(1- Dimethylsulfamoyl- 1H-pyrrol- 3-yl)-2- hydroxy- ethylamino	H
380	2-(2- Chloro- phenyl)- ethoxy	H	H	H
381	H	H	4-(2-Amino- thiazol-5- ylmethoxy)- benzylamino	H

Ex. No.	R ²	R ³	R ⁴	R ⁸
382	H	H	4-(2,4,6-triamino-pyrimidin-5-ylmethyl)-benzylamino	H
383	2-[2-(2,5-Dioxo-imidazolidin-4-yl)-acetylamo]ethoxy	H	H	H
384	4-benzylcarbamoyl-methoxy	H	H	H
385	H	H	NH-SO ₂ -CH ₃	H
386	2-[(Pyridine-3-carbonyl)-amino]ethoxy	H	H	H
387	Ph- <i>m</i> -NH ₂	H	Cl	H
388	-Ph- <i>m</i> -(NH-SO ₂ -CH ₃)	H	Cl	H
389	Br	H	-CH ₂ CH ₂ COOH	H
390	Br	H	2-[2-(2,4-Dichlorophenyl)-ethylcarbamoyl]-ethyl	H
391	Br	H	CH ₂ CH ₂ COOCH ₃	H
393	1-(3-Amino-propionyl)-pyrrolidin-2-ylmethoxy	H	H	H

Ex. No.	R ²	R ³	R ⁴	R ⁸
394	[(Tetrahy- dro- furan-2- ylmethyl) - carbamoyl]-methoxy	H	H	H
395	OCH ₂ CO ₂ H	H	H	H
396	4,5,6,7- Tetrahydr o-3H- imidazo[4 ,5- c]pyridin -2-yl	H	H	H
397	piperidin e-3-yl	H	Cl	H
298	5- Carbamimi doyl- 4,5,6,7- tetrahydr o-3H- imidazo[4 ,5- c]pyridin -2-yl	H	H	H
399	1-(2- Amino-3- methyl- butyryl)- pyrrolidi n-2- ylmethoxy	H	H	H
400	1-(2- Amino-3- methyl- butyryl)- pyrrolidi n-2- ylmethoxy	H	H	H

Ex. No.	R ²	R ³	R ⁴	R ⁶
401	5-Aminoacet yl- 4,5,6,7-tetrahydr o-3H-imidazo[4 ,5- c]pyridin -2-yl	H	H	H
402	5-(3-Amino- propionyl)- 4,5,6,7- tetrahydro- 3H-imidazo[4,5 -c]pyridin- 2-yl	H	H	H
403	1-(2-Amino- 1-imino- ethyl)- piperidin- 3-yl	H	Cl	H
404	H	H	4-(4-[phenylmeth yl amino]- phenoxy)- piperidine- 1- carboxylic acid tert- butyl ester	H
405	2-(3-Biphenyl- 2-yl- ureido)- ethoxy	H	H	H
406	O(CH ₂) ₂ - NH-C(O)- CH, OCH ₃	H	H	H
407	H	H	4-(Piperidin- 4-yloxy)- benzylamino	H
408	H	H	4-(Piperidin- 3- ylmethoxy)- benzylamino	H

Ex. No.	R ²	R ³	R ⁴	R ⁸
409	H	3-(3,4-Dichlorobenzoylaminoo)-propoxy	H	H
410	H	Pyrrolidin-2-ylmethoxy	H	H
411	H	(Benzyl-methyl-carbamoyl)-methoxy	H	H
412	H	OCH ₂ C(O)NH-(CH ₂) ₂ Ph	H	H
413	Br	(2,3-Dichlorobenzylcarbamoyl)-methoxy	Br	H
414	H	H	4-(pyrrolidin-3-yloxy)-benzylamino	H
415	H	H	4-[1-(1-Imino-ethyl)-piperidin-4-yloxy]-benzylamino	H
416	H	H	4-(2-Acetylamino-thiazol-5-ylmethoxy)-benzylamino	H
417	H	H	4-[1-(1-Imino-ethyl)-pyrrolidin-2-ylmethoxy]-benzylamino	H
418	H	H	3-[1-(1-Imino-ethyl)-pyrrolidin-3-yloxy]-benzylamino	H

Ex. No.	R ²	R ³	R ⁴	R ⁸
419	H	2-(3-bromo-benzoylamino)-ethoxy	H	H
420	H	2-(3,5-Dichloro-benzoylamino)-ethoxy	H	H
421	H	2-[(Naphthalene-2-carbonyl)-amino]-ethoxy	H	H
422	Br	H	2-Phenyl carbamoyl-ethoxy	H
423	O(CH ₂) ₂ -NH-C(O)CH ₂ NH-COO-C(CH ₃) ₃	H	H	H
424	O(CH ₂) ₂ -NH-C(O)NH-CH ₂ -Ph	H	H	H
425	O(CH ₂) ₂ -NH-C(O)CH ₂ NH ₂	H	H	H
426	O(CH ₂) ₂ -NH-C(O)CH ₂ -Ph	H	H	H
427	O(CH ₂) ₂ -NH-C(O)(CH ₂) ₂ -Ph	H	H	H
428	3-Amino-benzylxy	H	H	H
429	Br	OH	Br	H
430	H	H	3-(4-Amino-cyclohexyloxy)-benzylamino	H

Ex. No	R ²	R ³	R ⁴	R ⁸
431	H	H	3-[4-(methylamino)-phenoxy]-pyrrolidine-1-carboxylic acid tert-butyl ester	H
e32	Br	H	2-[(benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-ethyl	H
333	Br	H	2-(2-Morpholin-4-yl-ethylcarbamoyl)-ethyl	H
e34	Br	H	2-Benzylcarbamoyl-ethyl	H
e35	Br	H	Benzylcarbamoyl-methyl	H
e36	Br	H	phenethylcarbamoyl-methyl	H
e37	Br	H	(2-Hydroxyethylcarbamoyl)-methyl	H
438	Br	H	tetrahydrofuran-2-ylmethylcarbamoyl-methyl	H
439	Br	H	Benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-methyl	H
440	Br	H	2-(3-Chlorobenzylcarbamoyl)-ethyl	H
441	Br	H	2-(4-Chlorobenzylcarbamoyl)-ethyl	H
442	Br	H	2-(Methylphenethylcarbamoyl)-ethyl	H

Ex. No	R ²	R ³	R ⁴	R ⁸
3443	Br	H	2- Methylcarba moyl-ethyl	H
444	Br	H	2- dimethylcar bamoyl- ethyl	H
445	3- aminophenyl	H	2-carboxy- ethyl	H
446	3- nitrophenyl	H	2-carboxy- ethyl	H
447	3- aminophenyl	H	2- Phenethylca rbamoyl- ethyl	H
448	Br	H	2- Phenethylca rbamoyl- ethyl	H
449	Cl	H	2- Benzylcarba moyl-ethyl	H
450	Cl	H	2- Phenethylca rbamoyl- ethyl	H
451	Cl	H	3-(3,4- Dihydro-1H- isoquinolin -2-yl)-3- oxo-propyl	H
452	Cl	H	2-(2,2- Diphenyl- ethylcarbam oyl)-ethyl	H
453	Cl	H	CH ₂ CH ₂ COOH	F
454	Cl	H	2- [(naphthale n-1- ylmethyl)- carbamoyl]- ethyl	H
455	Br	H	2-tert- Butoxycarbo nylamino- ethyl	H
456	Cl	H	2- (Benzhydryl- carbamoyl)- ethyl	H

Ex. No	R ²	R ³	R ⁴	R ⁸
357	Br	H	2-amino-ethyl	H
458	Cl	H	2-[(Furan-2-ylmethyl)-carbamoyl]-ethyl	H
459	Br	H	3-(4-Chlorobenzenesulfonylamino)-3-oxo-propyl	H
460	Br	H	2-Phenylmethanesulfonfonylaminoo-ethyl	H
461	Br	H	2-(Naphthalene-2-sulfonylamino)-ethyl	H
462	Cl	H	2-(3,5-dimethoxybenzylamino)-ethyl	H
		H		

* R⁷ = C(=O)NH₂

Spectral data for compounds listed in Table 2 above is provided below:

Ex. 301

5 Mass, MS (ESI) 481.11 (calc.); 482.2. (obs.)

Ex. 308

¹H NMR (DMSO-d₆) δ: 9.50 (s, 2H), 9.24 (s, 2H), 8.4-8.1 (br m, 2H), 8.00- 7.86 (m, 2H), 7.79 (d, 1H, J = 9 Hz), 7.26 10 (t, 1H, J = 9 Hz), 7.02 (t, 1H, 9Hz), 5.19 (d, 1H, J = 22 Hz), 4.25-3.25 (br.m), 2.12-2.00 (br m, 2H).

MS (ESI): 394.18 (calc.); 394.9 (obs.).

Ex. 312

15 ¹H-NMR (methanol-d₄) δ ppm: 9.55 (s, 2H), 9.05 (s, 2H), 8.35 (s, 1H), 8.07 (d, 1H J = 8 Hz), 7.95, (d, 1H, J = .8 Hz), 7.69 (d, 1H, J = 8 Hz), 7.40 (d, 1H, J = 8 Hz), 7.17 (t, 1H, J = 8 Hz), 4.20-4.00 (m, 3H), 3.88 (br.d, 1H), 3.32 (m, 1H), 3.25-3.05 (m, 2H), 2.40 (br.m, 1H), 2.08 (br.m, 20 1H), 1.90 (br.m, 1H).

MS (Bioion): 407.21 (calc.); 408 (obs.)

EX. 325

¹H NMR (DMSO-d₆) δ: 9.41 (br.s, 2H), 9.05 (br.s, 2H), 8.22 (s, 1H), 7.90 (d, 1H, J = 8.5 Hz), 7.83 (d, 1H, J = 8.0 hz), 7.75 (d, 1H, J = 8.5 Hz), 7.18 (d, 1H, J = 8.0 Hz), 7.01 (t, 1H, J = 8.0 Hz), 4.63 (s, 2H), 3.42 (m, 2H), 2.73 (t, 2H, J = 6.4 Hz).

MS: 378.14 (calc.); 379.2 (obs.).

30

Ex. 330

¹H-NMR (DMSO-d₆) δ ppm: 9.54 (s, 2H), 9.26 (s, 2H), 8.27 (s, 1H), 7.94 (m, 2H), 7.81 (d, 1H, J = 8.6 Hz), 7.26 (d, 1H, J = 8.1 Hz), 7.03 (t, 1H, J = 8.1 Hz), 4.65 (s, 2H), 3.95-35 3.78 (m, 4H), 3.60-3.47 (m, 4H), 3.27-3.10 (m, 4H).

MS (ESI, M⁺ +1): Calc. 438.20; Found 439.1.

EX. 332

¹H NMR (DMSO-d₆) δ: 9.53 (br.s, 2H), 9.23 (br.s, 2H), 8.28 (s, 1H), 7.97 (d, 1H, J = 8.5 Hz), 7.92 (d, 1H, J = 8.1 Hz), 5 7.84 (d, 1H, J = 8.5 Hz), 7.28 (d, 1H, J = 8.1 Hz), 7.05 (t, 1H, J = 8.1 Hz), 4.60 (s, 2H), 3.25-3.15 (m, 4H), 1.80 (s, 3H).

MS: 410.17 (calc.); 411.0 (obs.).

10

Ex. 333

¹H NMR (CD₃OD) δ: 9.45 (s, 2H), 9.15 (s, 2H), 8.38-8.26 (m, 1H), 8.22 (s, 1H), 7.95-7.78 (m, 2H), 7.51 (d, 1H, J = 10 Hz), 7.27 (d, 1H, 14 Hz), 6.98 (t, 1H, H = 14 Hz), 4.40-4.29 (m, 1H), 4.29-4.20 (d, 1H, J = 12 Hz), 4.02 (t, 1H, J = 9 Hz), 3.85-3.40 (br.m), 2.40-1.80 (br.m, 8H), 0.95 (m, 9H).

MS: 450.24 (calc.); 451.1 (obs.).

Ex. 335

20 ¹H NMR (DMSO-d₆) δ: 9.34 (br.s, 2H), 8.96 (br.s, 2H), 8.20 (s, 1H), 7.88 (d, 1H, J = 8.5 Hz), 7.80 (d, 1H, J = 7.9 Hz), 7.71 (d, 1H, J = 8.5 Hz), 7.14-6.95 (m, 6H), 4.56 (s, 2H), 3.40 (t, 2H, J = 7.5 Hz), 2.71 (t, 2H, J = 7.5 Hz), 2.22 (s, 3H).

25 MS: 443.2 (calc.); 444.1 (obs.).

Ex.: 337

¹H NMR (DMSO-d₆) δ: 9.55 (2H, br.s), 9.26 (2H, br.s), 8.28 (1H, s), 7.98-7.82 (3H, m), 7.27 (1H, d, J= 8.0 hz), 7.07-30 6.92 (3H, m), 6.83 (1H, d, J = 7.4 Hz), 4.69 (2H, s), 4.40 (2H, s), 3.78 (3H, s), 3.74 (2H, s).

MS(ES): Calc: 475.19; Obs.: 475.7.

Ex. 346

¹H-NMR (DMSO-d₆) δ ppm: 9.45 (sm 1H), 9.15 (s, 1H), 8.4-8.05 (m, 4H), 8.0-7.7 (m, 4H), 7.4-7.25 (m, 1H), 7.05 (m, 1H), 4.5-3.5 (m), 3.2-2.7 (m, 2H), 2.2-1.3 (m, 7H).

MS (ESI): 422.9 (calc.); 422.21 (obs.)

5

Ex. 353

¹H NMR (CD₃OD) δ: 9.39 (s, 2H), 9.04 (s, 2H), 8.21 (s, 1H), 8.08 (s, 1H), 8.03 (m, 1H), 7.88 (d, 1H, J = 8.4 Hz), 7.76 (d, 1H, J = 8.4 Hz), 7.61 (s, 1H), 7.15 (m, 4H), 3.25 (br. m, 2H), 2.85 (br.m, 2H), 2.61 (t, 2H, J = 7.2 Hz), 2.46 (br.m, 2H).

MS (LRMS) M+1: Calc: 505.11; Obs.: 506.06.

Ex.: 354

15 ¹H NMR (DMSO-d₆) δ: 9.47 (s, 2H), 9.15 (s, 2H), 8.24 (s, 1H), 7.94-7.77 (m, 5H), 7.53-7.44 (m, 3H), 7.30 (d, 1H, J = 8.1 Hz), 7.02 (t, 1H, J = 8.1 Hz), 4.20 (t, 2H, J = 5.7 Hz), 3.70 (m, 2H).

MS (ESI, M⁺ +1): Calc. 415.16; Found 416.2.

20

Ex. 355

25 ¹H NMR (DMSO-d₆) δ: 9.49 (s, 2H), 9.17 (s, 2H), 8.25 (s, 1H), 7.94 (d, 1H, J = 8.6 Hz), 7.82 (m, 2H), 7.25 (d, 1H, J = 7.7 Hz), 7.04 (t, 1H, J = 7.7 Hz), 4.06 (t, 2H, J = 5.4 Hz), 3.46 (m, 2H), 2.30 (m, 4H).

MS (ESI, M⁺ +1): Calc. 410.17; Found 411.1.

30

Ex. 360

¹H-NMR (DMSO-d₆) δ: 9.35 (s, 2H), 8.94 (s, 2H), 8.19 (s, 1H), 7.86-7.70 (m, 3H), 7.17 (d, 1H, J = 8.1 Hz), 6.98 (t, 1H, J = 8.1 Hz), 4.63 (s, 2H), 3.82 (s, 2H), 1.39 (s, 9H).

MS (ESI, M⁺ +1): Calc. 439.19; Found 440.1.

35

Ex. 361

¹H-NMR (methanol-d₄) δ ppm: 9.55 (s, 0.5 H), 9.10 (s, 0.5H), 8.35 (s, 1H), 8.09 (d, 1H), 8.00 (d, 1H), 7.71 (d, 1H), 7.52 (d, 1H), 7.20 (t, 1H), 4.1 (br.m, 1H), 4.41 (m, 1H),

4.22 (m, 1H), 4.1 (m, 1H), 3.50 (m, 2H), 3.35 (m, 1H), 2.07 (m, 5H).

MS (ESI): 409.18 (calc.), 410.0 (obs.)

5

Ex. 367

MS: 380.16 (calc.); 381.0 (obs.).

Ex. 368

¹H-NMR (methanol-d₄) δ ppm: 8.40 (s, 1H), 8.09 (d, 1H),
10 8.00 (m, 1H), 7.71 (d, 1H), 7.59 (d, 1H), 7.20 (t, 1H),
4.51 (m, 2H), 4.09 (m, 2H), 3.80 (m, 1H), 3.65 (m, 1H),
3.33 (m, 2H), 2.40-2.00 (m, 6H), 1.45-1.25 (m, 4H), 1.19
(m, 6H).

MS (ESI): 450.24 (calc.), 451.2 (obs.)

15

Ex. 371

¹H NMR (DMSO-d₆) δ: 9.47 (s, 2H), 9.16 (s, 2H), 8.24 (s, 1H),
20 7.92 (d, 1H, J = 8.5 Hz), 7.78 (m, 2H), 7.23 (d, 1H, J =
7.3 Hz), 7.01 (t, 1H, J = 7.3 Hz), 4.06 (t, 2H, J = 5.4
Hz), 3.50 (m, 2H), 2.64 (m, 2H), 2.50 (m, 2H).

MS (ESI, M⁺ +1): Calc. 392.16; Found 393.2.

25

EX. 373

¹H NMR (DMSO-d₆) δ: 9.4 (br.s, 2H), 9.03 (br.s, 2H), 8.22 (s,
1H), 7.91-7.73 (m, 3H), 7.18 (d, 1H, J = 8.1 Hz), 7.00 (t,
1H, j = 8.1 Hz), 4.57 (s, 2H), 3.18 (t, 2H, J = 7.2 hz),
1.55 (m, 1H), 1.35 (m, 2H), 0.86 (d, 6H, J = 6.6 hz).

30 MS: 395.2 (calc.); 396.1 (obs.).

Ex. 374

¹H NMR (DMSO-d₆) δ: 9.45 (s, 2H), 9.11 (s, 2H), 8.24 (s, 1H),
35 7.93-7.76 (m, 5H), 7.62-7.57 (m, 3H), 7.11 (d, 1H, J = 8.1
Hz), 6.98 (t, 1H, J = 8.1 Hz), 4.03 (t, 2H, J = 5.4 Hz),
3.18 (t, 2H, J = 5.4 Hz).

MS (ESI, M⁺ +1): Calc. 451.13; Found 452.1.

Ex. 378

¹H-NMR (methanol-d₄) δ ppm: 9.6 (s, 2H), 9.09 (s, 1H), 8.36 (s, 1H), 8.18 (d, 1H, J = 8 Hz), 8.00 (d, 1H, J = 8 Hz), 5 7.70 (d, 1H, J = 8 Hz), 7.57 (d, 1H, 8 Hz), 7.16 (t, 1H, J = 8 Hz), 4.55 (m, 1H), 4.43 (dd, 1H), 4.07 (t, 1H), 3.70-3.40 (m, 2H), 3.24 (m, 1H), 2.80 (t, 2H), 2.3-2.0 (m, 5H). MS (ESI): 422.21 (calc.), 423.1 (obs.)

10

Ex. 380

¹H-NMR (DMSO-d₆) δ: 9.40 (s, 2H), 9.06 (s, 2H), 8.20 (s, 1H), 7.87-7.72 (m, 3H), 7.53-7.19 (m, 5H), 6.97 (t, 1H, J = 7.9 Hz), 4.27 (t, 2H, J = 7.1 Hz), 3.21 (t, 2H, J = 7.1 Hz). 15 MS (ESI, M⁺ +1): Calc. 406.12; Found 407.0.

Ex. 383

¹H NMR (DMSO-d₆) δ: 9.41 (s, 2H), 9.06 (s, 2H), 8.21 (s, 1H), 20 7.88 (d, 1H, J = 8.4 Hz), 7.77 (m, 2H), 7.21 (d, 1H, J = 7.8 Hz), 7.00 (t, 1H, J = 7.8 Hz), 4.22 (dd, 1H, J = 7.1, 4.2), 4.06 (t, 2H, J = 5.5 Hz), 3.47 (t, 1H, J = 5.5 Hz) 2.56 (m, 2H). MS (ESI, M⁺ +1): Calc. 451.16; Found 452.3.

25

Ex. 384

¹H NMR (DMSO-d₆) δ: 9.45 (br.s, 2H), 9.11 (br.s, 2H), 8.24 (s, 1H), 7.94-7.76 (m, 3H), 7.35-7.22 (m, 6H), 7.03 (t, 1H, J = 8.1 Hz), 4.68 (s, 2H), 4.40 (s, 2H). 30 MS: 415.16 (calc.); 416.1 (obs.).

Ex. 385

¹H NMR (DMSO-d₆) δ: 9.51 (s, 1H), 9.29 (br.s, 2H), 9.03 (br.s, 2H), 8.18 (s, 1H), 8.02 (s, 1H), 7.83 (d, 1H, J = 7 Hz), 7.70 (d, 1H, J = 7 Hz), 7.25 (dd, 1H) 7.09 (d, 1H, J = 7 Hz), 2.96 (s, 3H). MS: 345.09 (calc.); 345.9 (obs.).

Ex. 386

5 ^1H NMR (DMSO-d₆) δ : 9.46 (s, 2H), 9.23 (s, 1H), 9.14 (s, 2H),
 8.88 (d, 1H, J = 5.3 Hz), 8.67 (d, 1H, J = 8.0 Hz), 8.23
 (s, 1H), 7.92-7.76 (m, 4H), 7.28 (d, 1H, J = 8.0 Hz), 7.01
 (t, 1H, J = 8.0 Hz), 4.23 (t, 2H, J = 5.5 Hz), 3.74 (m,
 2H).

10 MS (ESI, M⁺ +1): Calc. 416.16; Found 417.1.

Ex. 387 2-(3'-Amino-5-chloro-2-hydroxy-biphenyl-3-yl)-3H-benzoimidazole-5-carboxamidine

15 $^1\text{H-NMR}$ (DMSO-d₆) δ ppm: 10.40 (br s, 2H), 9.44 (s, 2H),
 9.12 (s, 2H), 8.43 (s, 1H), 8.25 (s, 1H), 7.90 (d, 1H, J =
 7.6 Hz), 7.77 (d, 1H, J = 8.1 Hz), 7.70 (s, 1H), 7.65 (d,
 1H, J = 7.8 Hz), 7.57 (t, 1H, J = 7.9 Hz), 7.55 (s, 1H),
 7.38 (d, 1H, J = 7.4 Hz).

20 MS (CI): Calc. 377.1, Found 378.6.

Ex. 388

15 $^1\text{H-NMR}$ (DMSO-d₆) δ ppm: 9.88 (s, 1H), 9.42 (s, 2H), 9.11
 (s, 2H), 8.38 (s, 1H), 8.24 (s, 1H), 7.90 (d, 1H, J = 8.3
 Hz), 7.77 (d, 1H, J = 8.4 Hz), 7.50-7.30 (m, 4H), 7.23 (d,
 1H, J = 7.5 Hz), 3.05 (s, 3H).

25 MS (ESI, M+1): Calc. 455.1, Found 456.0.

Ex. 389

15 $^1\text{H-NMR}$ (DMSO-d₆) δ ppm: 9.41 (s, 2H), 9.09 (s, 2H), 8.23
 (s, 1H), 8.15 (s, 1H), 7.87 (d, 1H, J= 8.43 Hz), 7.74 (d,
 1H, J= 8.43 Hz), 7.66 (s, 1H), 2.84 (t, 2H, J= 7.4 Hz),
 2.63 (t, 2H, J= 7.4 Hz).

25 MS (ESI, M+1): Calc. 402.03, Found 403.1

Ex. 393 2-[3-(1-Aminoacetyl-pyrrolidin-2-ylmethoxy)-2-hydroxy-phenyl]-3H-benzoimidazole-5-carboxamidine

35 MS: 408.19 (calc.) ; 409.0 (obs.)

40

Ex.: 394

5 ^1H NMR (DMSO-d₆) δ : 9.45 (2H, br.s), 9.14 (2H, br.s), 8.25
 (1H, s), 7.94-7.77 (3H, m), 7.22 (1H, d, J = 8.0 Hz), 7.02
 (1H, s, J = 8.0 Hz), 4.62 (2H, s), 3.87-3.56 (4H, m), 3.24
 (2H, m), 1.80 (2H, m), 1.50 (1H, m).
 MS(ES): Calc.: 409.18; Obs.: 410.0.

Ex. 395

10 ^1H NMR (DMSO-d₆) δ : 9.48 (br.s, 2H), 9.18 (br.s, 2H), 8.25 (s,
 1H), 7.95-7.77 (m, 3H), 7.11 (d, 1H, J = 8.1 hz), 7.00 (t,
 1H, J = 8.1 Hz), 4.82 9s, 2H).
 MS: 326.10 (calc.) 326.8 (obs.).

15

Ex. 396

10 ^1H NMR (DMSO-d₆) δ : 10.15 (s, 1H); 10.05 (s, 1H); 9.5 (s,
 2H); 9.2 (s, 2H); 8.6 (d, 1H); 8.3 (s, 1H); 7.9 (d, 1H);
 7.8 (d, 1H); 7.3 (t, 1H); 4.19 (s, 2H); 3.5 (t, 2H); 3.05
 (t, 2H).
 MS: 373.17 (calc); 374.5 (obs.).

Ex. 398

25 ^1H NMR (DMSO-d₆) δ : 9.45 (s, 2H), 9.1 (s, 2H), 8.45 (d, 1H);
 8.25 (s, 1H); 8.23 (d, 1H); 7.85 (s, 3H); 7.83 (d, 1H); 7.8
 (d, 1H); 7.3 (t, 1H); 4.75 (s, 2H); 3.8 (t, 2H); 2.9 (t,
 2H).
 MS: 415.19 (calc.); 416.1 (obs.).

30

Ex. 399

10 $^1\text{H-NMR}$ (methanol-d₄) d ppm: 8.36 (s, 1H), 8.07 (d, 1H, J =
 8 Hz), 7.98 (d, 1H, J = 8 Hz), 7.70 (d, 1H, J = 8 Hz), 7.52
 (1H, d, J = 8 Hz), 7.16 (t, 1H, J = 8 Hz), 4.58 (p, 1H),
 4.36 (m, 1H), 4.20-4.10 (m, 2H), 3.80-3.60 (m, 2H), 3.30
 (m, 1H), 2.40-2.00 (m, 6H), 1.41 (d, 1H), 1.32 (s, 1H),
 1.13 (d, 3H), 1.03 (d, 3H).
 MS (ESI): 450.24 (calc.), 451.2 (obs.)

Ex. 400

¹H NMR (CD₃OD) δ: 9.40 (s, 2H), 9.05 (s, 2H), 8.30 (br.s, 2H), 7.90-7.70 (m, 4H), 7.21 (d, 1H, J= 7 Hz), 7.15-6.50 (t, 1H, J= 7 Hz), 4.40 (m, 1H), 4.20-4.07 (m, 2H), 4.07-3.95 (m, 1H), 3.75-3.60 (m, 1H), 3.60-3.25 (m, 6H), 2.10-1.80 (m, 6H), 0.95 (t, 3H), 0.85 (t, 3H).

MS (ESI): Calc.: 450.24; Obs.: 451.1.

Ex. 401

10 MS (ES): 430.19 (calc.); 429.0 (obs.).

Ex. 402

MS (ES): Calc.: 444.2 ; Obs.: 444.9.

15 **Ex. 403**

MS: 426.2 (calc.); 427.0 (obs.).

Ex. 405

20 ¹H-NMR (DMSO-d₆) δ: 9.38 (s, 2H), 9.03 (s, 2H), 8.20 (s, 1H), 7.88-7.75 (m, 4H), 7.45-6.99 (m, 10H), 4.04 (t, 2H, J = 5.5 Hz), 3.44 (m, 2H).

MS (ESI, M⁺ +1): Calc. 506.21; Found 507.2.

25

Ex. 406

30 ¹H NMR (DMSO-d₆) δ: 9.58 (s, 2H), 9.29 (s, 2H), 8.29 (s, 1H), 7.98 (d, 1H, J = 9.1 Hz), 7.86 (m, 2H), 7.27 (d, 1H, J = 7.8 Hz), 7.04 (t, 1H, J = 7.8 Hz), 4.09 (t, 2H, J = 5.5 Hz), 3.84 (s, 2H), 3.57 (m, 2H) 3.30 (s, 3H).

MS (ESI, M⁺ +1): Calc. 383.16; Found 384.0.

35

Ex. 423

40 ¹H NMR (DMSO-d₆) δ: 9.42 (s, 2H), 9.10 (s, 2H), 8.22 (s, 1H), 7.90-7.74 (m, 3H), 7.20 (d, 1H, J = 7.8 Hz), 7.00 (t, 1H, J = 7.8 Hz), 4.06 (m, 2H), 3.50 (m, 4H), 1.35 (s, 9H).

MS (ESI, M⁺ +1): Calc. 468.21; Found 469.2.

Ex. 424

5 ^1H NMR (DMSO-d₆) δ : 9.43 (s, 2H), 9.10 (s, 2H), 8.22 (s, 1H),
6H), 7.89 (d, 1H, J = 8.5 Hz), 7.81-7.75 (m, 2H), 7.30-7.18 (m,
6H), 7.00 (t, 1H, J = 8.1 Hz), 4.22 (s, 2H), 4.05 (t, 2H, J
= 5.5 Hz), 3.43 (t, 2H, J = 5.5 Hz).
MS (ESI, M⁺ +1): Calc. 444.19; Found 445.2.

10

Ex. 425

15 ^1H NMR (DMSO-d₆) δ : 9.36 (s, 2H), 9.07 (s, 2H), 8.72 (m, 1H),
8.19 (s, 1H), 7.84 (d, 1H, J = 8.6 Hz), 7.76 (m, 2H), 7.18
(d, 1H, J = 8.1 Hz), 6.98 (t, 1H, J = 8.1 Hz), 4.10 (t, 2H,
J = 5:4), 3.57 (m, 4H).
MS (ESI, M⁺ +1): Calc. 368.16; Found 369.0.

20

Ex. 426

25 ^1H NMR (DMSO-d₆) δ : 9.45 (s, 2H), 9.13 (s, 2H), 8.24 (s, 1H),
7.91 (d, 1H, J = 8.5 Hz), 7.83 (m, 2H), 7.27-7.20 (m, 6H),
7.00 (t, 1H, J = 8.1 Hz), 4.08 (t, 2H, J = 5.6 Hz), 3.48
(m, 2H), 3.46 (s, 2H).
MS (ESI, M⁺ +1): Calc. 429.18; Found 430.1.

30

Ex. 427

35 ^1H NMR (DMSO-d₆) δ : 9.46 (s, 2H), 9.15 (s, 2H), 8.24 (s, 1H),
7.90 (d, 1H, J = 8.5 Hz), 7.80 (m, 2H), 7.24-7.12 (m, 6H),
7.00 (t, 1H, J = 8.0 Hz), 4.02 (t, 2H, J = 5.6 Hz), 3.46
(m, 2H), 2.82 (t, 2H, J = 7.3 Hz), 2.41 (t, 2H, J = 7.3
Hz).
MS (ESI, M⁺ +1): Calc. 443.20; Found 444.1.

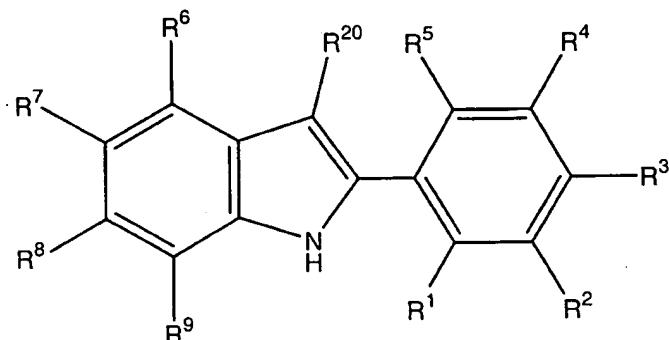
40

Ex. 428

45 ^1H NMR (DMSO-d₆) δ : 9.41 (s, 2H), 9.08 (s, 2H), 8.22 (s, 1H),
7.88-7.73 (m, 3H), 7.50 (m, 3H), 7.32 (m, 1H), 7.24 (d, 1H,
J = 8.0 Hz), 6.98 (t, 1H, J = 8.0 Hz), 5.26 (s, 2H).
MS (ESI, M⁺ +1): Calc. 373.15; Found 374.0.

SYNTHESIS OF INDOLE BASED COMPOUNDS OF FORMULA I

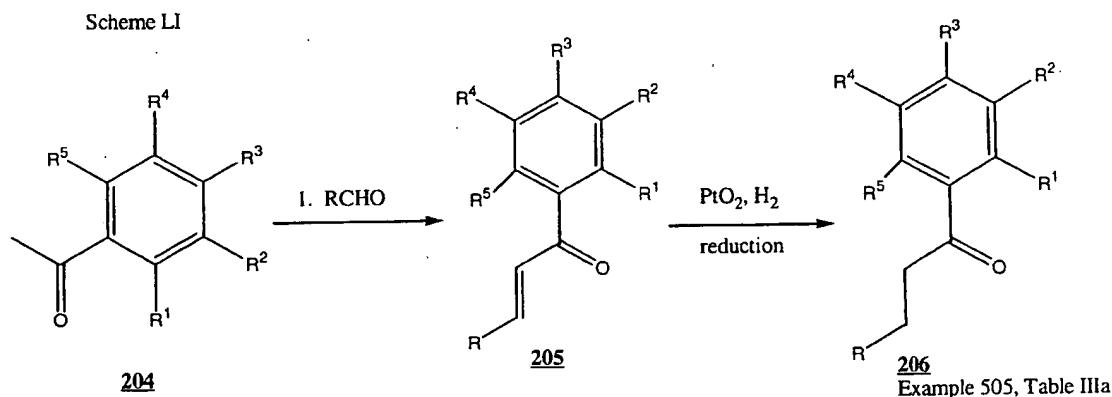
5 Procedures LI through LXI discuss the synthesis of precursors useful in synthesizing indole based compounds of Formula I. These indole based compounds of Formula I can be structurally represented as follows.



10 wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and R²⁰ are as described in the detailed description.

Compounds of Formula I having the indole nucleus can be synthesized by using commercially available ketones or carboxylic acids, for example compounds 210 to 237, and aldehyde compounds 240(a) to 240(e) which can be prepared by schemes LI through LXI. discussed below.

Scheme LI



20

Scheme LI illustrates the general procedure for condensation of acetophenones and substituted aromatic

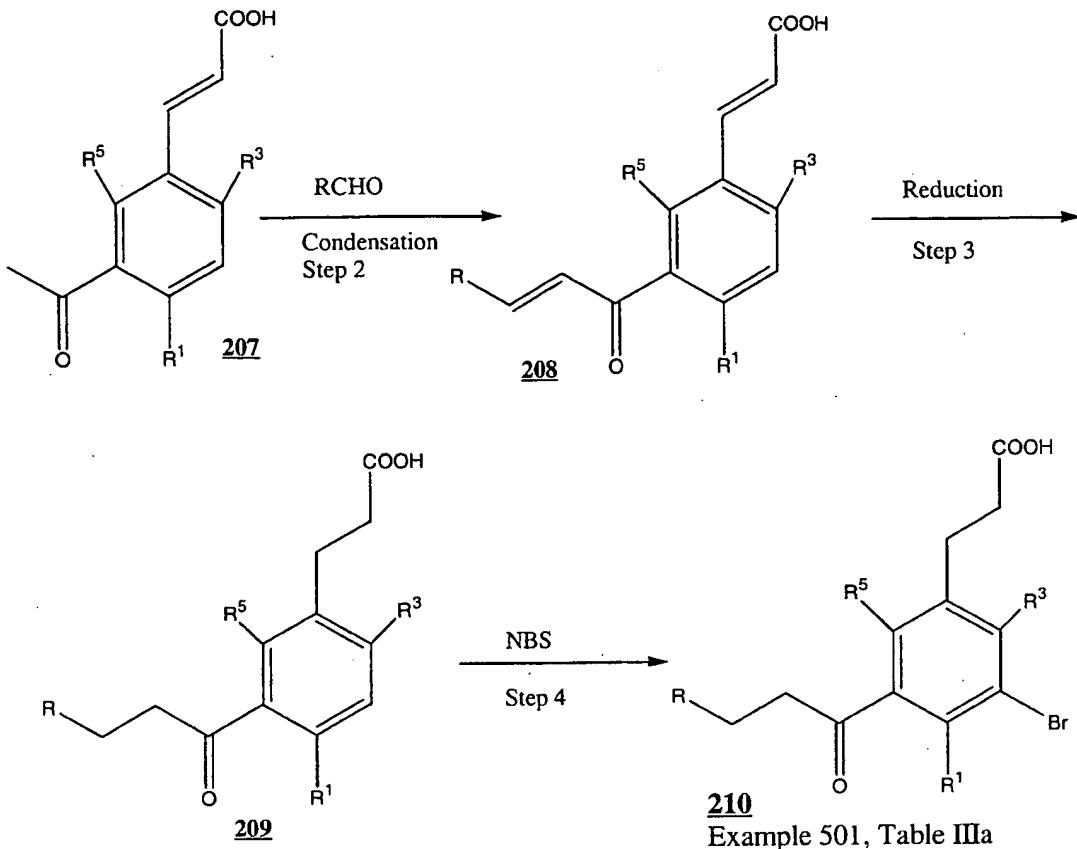
aldehydes, wherein R¹, R², R³, R⁴ and R⁵ are as described in the detailed description section above.

Compounds of Formula 201 wherein R²⁰ is CH₂R can be prepared by methods illustrated by Scheme LI. For example compound 204 wherein R¹ is hydrogen, R² and R⁴ are fluoro and R³ is hydrogen, i.e., 1-(3,5-difluoro-2-hydroxyphenyl)ethanone 204 (6.3 mmol) and benzaldehyde (7.56 mmol) are mixed in ethanol (20 mL) and aqueous barium hydroxide (2 gm in 15 mL water) (aqueous NaOH (10 %) may be substituted for barium hydroxide) is added. The mixture is stirred for 12-18 h at 60° (reaction times can vary between 3 h to 18 h). The mixture was filtered and the solids which were collected were washed with water (30 mL) and ether (20 mL). The solids are taken up in 1N HCl (30 mL) and the solution extracted with ethyl acetate. The organic extracts are washed with water, brine and dried (MgSO₄) to afford 1-(3,5-difluoro-2-hydroxyphenyl)-3-propenone the title compound 205 as a yellow-brown solid in a 70% yield.

1-(3,5-difluoro-2-hydroxyphenyl)-3-propenone 205 was catalytically hydrogenated using PtO₂-C (10%) as a catalyst (can substitute Pd-C or Pd(OH)₂ as catalysts) and ethyl acetate as a solvent for 15 min (or until reduction is completed). The catalyst was filtered off and the filtrate was evaporated to yield 1-(3,5-difluoro-2-hydroxyphenyl)-3-propan-1-one 206 (Example 505, Table IIIa).

30

35 Scheme LII



Scheme LII illustrates synthesis of ketones 210, wherein R¹, R², R³, and R⁵ are as defined in the detailed description section above.

For example 1-(5-bromo-2-hydroxy phenyl)ethanone 206 (6.6 g, 30.7 mmol), methyl acrylate (4.17 mL, 46 mmol), triphenyl phosphine (2.43 g, 9 mmol), palladium acetate (1.03 g, 4.6 mmol), and triethyl amine (6.07 g, 60 mmol) were combined with benzene (100 mL) and refluxed over 18 h. The reaction mixture is cooled to room temperature, diluted with 0.05 N HCl (100 mL) and extracted with ethyl acetate. The organic layer is separated and further washed with water and then brine solution. The organic layer is dried (MgSO₄), and concentrated to yield an oily residue. Purification of this residue by column chromatography (10:1.5, hexanes: ethyl acetate) afforded 5-(2-carboxy vinyl-2-hydroxy)benzoic acid 207 as a yellow solid.

¹H NMR (CDCl₃, 300 MHz) δ: 12.22 (s, 1H), 8.23 (s, 1H), 7.94 (d, 1H, J = 8.7 Hz), 7.67 (d, 1H, J = 16 Hz), 7.0 (d, 1H, J = 8.7 Hz), 6.8 (d, 1H, J = 16 Hz).

5 5-(2-carboxy vinyl-2-hydroxy)benzoic acid **207** was converted to 3-[4-yydroxy-3-(3-phenyl-acryloyl)-phenyl]-acrylic acid as described by general condensation procedure in Scheme LI above, to yield **208**.

10 ¹H NMR (DMSO-d₆) δ: 12.81 (s, 1H), 8.54 (s, 1H), 8.12 (d, 1H, J = 5.5 Hz), 7.91 (m, 4H), 7.67 (d, 1H, J = 16.0 Hz), 7.49 (m, 3H), 7.04 (d, 1H, J = 8.7 Hz), 6.57 (d, 1H, J = 6.0 Hz).

MS(M⁺) : Calc.: 294.3; Obs.: 294.5.

15 3-[4-Hydroxy-3-(3-phenyl-acryloyl)-phenyl]-acrylic acid was converted to 3-[4-hydroxy-3-(3-phenyl-propionyl)-phenyl]-propionic acid **209** as described by general reduction procedure in Scheme LI.

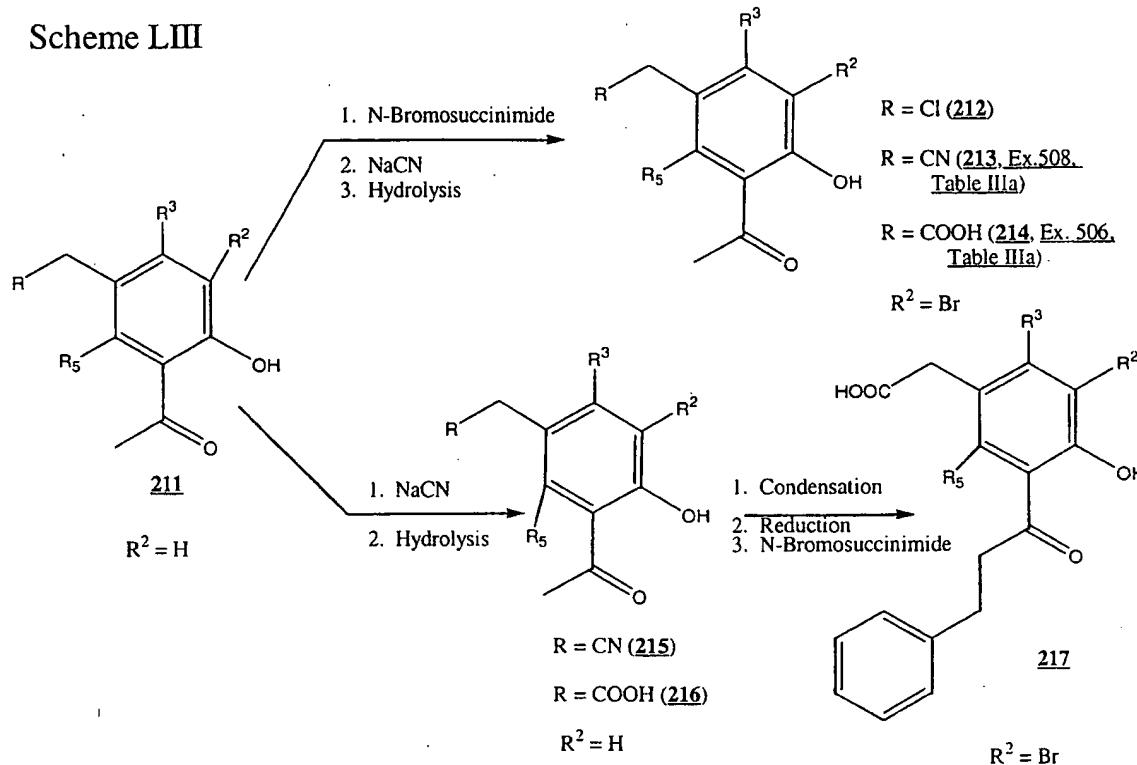
General procedure for brominating at position R².

20 The carboxylic acid **209**, for example 3-[4-Hydroxy-3-(3-phenyl-propionyl)-phenyl]-propionic acid, (1.04 gm, 3.4 g mmol) was dissolved in DMF (7 mL) and N-bromosuccinimide (0.65 g, 3.66 mmol) was added to the solution. The mixture was stirred at ambient temperature for 2.5 h, diluted with 25 ether and the organic layer was separated and washed with water and brine and then filtered through a pad of magnesium sulfate and concentrated. The residue was purified by flash chromatography (3.5:1.5:0.1 of hexane:ethyl acetate:acetic acid) to give 0.5 g of 3-[3-bromo-4-hydroxy-5-(3-phenyl-propionyl)-phenyl]-propionic acid **210** as a yellow-brown oil.

30 ¹H NMR (CDCl₃) δ: 7.61 9 (d, 1H, J= 1.9 Hz), 7.54 (d, 1H, J= 1.9 Hz), 7.27 (m, 5H), 3.33 (t, 2H, J= 7.3 Hz), 3.06 (t, 2H, J= 7.8 Hz), 2.86 (t, 2H, J= 2,23 Hz), 2.64 (br.t, 2H).

35 LRMS M+1: Calc.: 376.03; Obs.: 377.9.

Scheme LIII



Scheme LIII illustrates the synthesis of ketones **212**

5 to **216**.

Preparation of 1-(5-chloromethyl-2-hydroxy-phenyl)-ethanone **211** was accomplished using the procedure of Florall, L; Ross, S.B et al., Acta Pharm. Suec, V 15, 1478, 10 p 13-22.

1-(3-Bromo-5-chloromethyl-2-hydroxy-phenyl)-ethanone **212**

A solution of N-bromosuccinimide (10 mmol) in 8 mL of DMF is added dropwise to a solution of 1-(5-chloromethyl-2-hydroxy-phenyl)-ethanone **211** (10 mmol) in 20 mL DMF and the resulting mixture is stirred for 12-18 h. The solvent is evaporated under reduced pressure and the residue is diluted with water resulting in the formation of a solid. The solid is isolated and recrystallized from ethanol to yield 1-(3-Bromo-5-chloromethyl-2-hydroxy-phenyl)-ethanone **212**.

¹H NMR (CDCl₃) δ ppm: 2.68 (s, 3H), 4.55 (s, 2H), 7.72 (q, 1H, J=2.1 Hz), 7.78 (q, 1H, J= 2.1 Hz), 13.02 (s, 1H).

MS : Found: 264; Calc.: 263.52

5 (3-acetyl-5-bromo-4-hydroxy-phenyl)-acetonitrile **213** (Ex. 508)

A solution of 1-(3-Bromo-5-chloromethyl-2-hydroxy-phenyl)-ethanone **212** (7.6 mmol) in 6 mL DMSO is added dropwise to a suspension of 8.2 mmol of NaCN in 4 mL DMSO.

10 The mixture is stirred for 12-18 h and diluted with 80 mL water to yield a solid. The solid is isolated and recrystallized from ethanol to yield (3-acetyl-5-bromo-4-hydroxy-phenyl)-acetonitrile **213** in a 58% yield.

¹H NMR (CDCl₃) δ ppm: 2.7 (s, 3H), 3.81 (s, 2H), 7.75 (s, 2H), 13.03 (s, 1H).

MS: Calc.: 244.08; Found: 255.0.

(3-Acetyl-5-bromo-4-hydroxy-phenyl)-acetic acid **214**
(Example 506, Table IIIa)

20 (3-acetyl-5-bromo-4-hydroxy-phenyl)-acetonitrile **213** (6 g, 23.6, mmol) is refluxed in a mixture of 50 mL acetic acid, 5 mL conc. H₂SO₄ and 5 mL water for about 2-3 h. This refluxed mixture is cooled to ambient temperature and poured onto ice forming a solid. The solid is isolated and recrystallized from a ethanol-water mixture to yield (3-acetyl-5-bromo-4-hydroxy-phenyl)-acetic acid **214** in a 47 % yield.

¹H NMR (CDCl₃) δ ppm: 2.67 (s, 3H), 3.59 (s, 2H), 7.62 (d, 1H, J= 1.9 Hz), 7.69 (d, 1H, J=1.9 Hz), 12.85 (s, 1H).

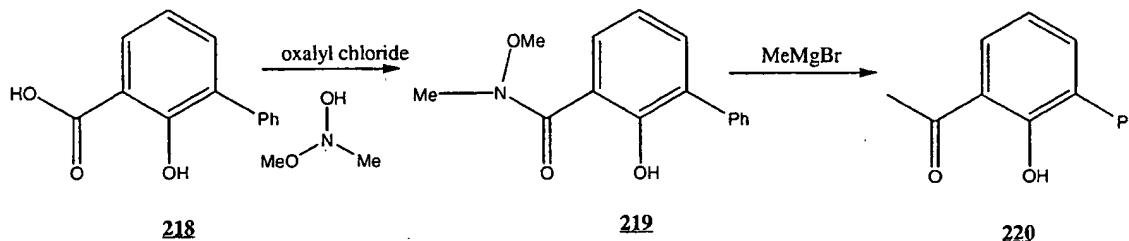
30 MS: Calc.: 273.08; Found: 274.0.

Synthesis of **215** and **216** can be accomplished by following the procedures outlined for **213** and **214** respectively.

Synthesis of 1-(3-acetyl-5-bromo-4-hydroxy-phenyl)-4-phenyl-butan-2-one **217** (Example 500, Table IIIa) is

accomplished from **216** following steps 2, 3 and 4 in Scheme LII above.

Scheme LIV



5

Scheme LIV illustrates synthesis of **220** which is useful in synthesizing compounds of Formula I.

219: 2-hydroxy-3-phenylbenzoic acid (**218**, 3.0 g, 14 mmol) is dissolved in EtOAc (50 ml) and a few drops of DMF are added. Oxalyl chloride (2.5 ml, 1.5 eq) is added and the reaction is stirred under a dry atmosphere for 1 h. The reaction mixture is then concentrated in vacuo to yield a mixture of clear oil and white solid. This mixture is diluted with CH₂Cl₂ (50 ml) followed by the addition of N,O-dimethyl hydroxylamine hydrochloride (1.5 g, 1.1 eq) and triethylamine (3.9 ml, 2 eq). This mixture is stirred for 12-18 h under a dry atmosphere. Dilution of the reaction mixture with EtOAc and subsequent washing with dilute HCl and brine, followed by drying (MgSO₄) and concentration in vacuo yields a mixture of reaction products. Flash chromatography (20/80 EtOAc/Hexanes) afforded N-methoxy-N-methyl-2-hydroxy-3-phenylbenzamide (**219**, 1.09g) as a white solid.

25 ¹H NMR (CDCl₃) δ: 11.42 (s, 1H) 7.94 (dd, 1 H, J = 1.7, 8.1 Hz) 7.61-7.58 (m, 1H) 7.48-7.36 (m, 6 H) 6.93 (t, 1 H, J = 2.3, 3.4 Hz) 3.70 (s, 3 H) 3.45 (s, 3 H).

220

30 N-methoxy-N-methyl-2-hydroxy-3-phenylbenzamide (**219**, 2.37 g, 9.2 mmol) is dissolved in dry THF (40 ml) under

nitrogen and cooled to 0°C in an ice bath. MeMgBr (6.5 ml, 2.1 eq) is added and the resulting heterogeneous reaction is stirred for 1 h, THF (50 ml) is added to facilitate stirring, followed by excess MeMgBr. The reaction is then 5 stirred for 3 days followed by quenching with dilute HCl. This mixture is then partitioned between ether and water. The organic phase is washed with brine, dried (MgSO_4) and concentrated in vacuo to yield a mixture of starting material (219) and product (220). Flash chromatography 10 (EtOAc/Hexanes) affords 2-hydroxy-3-phenylacetophenone (220, 0.78 g) as a white solid.

Example 522, Table IIIa: Prepared according to literature procedure: Sipos, G.; Szalo, R. Acta Physica et Chemica, 15 Vol. 7, 1961, pp. 126-128.

Example 503, Table IIIa

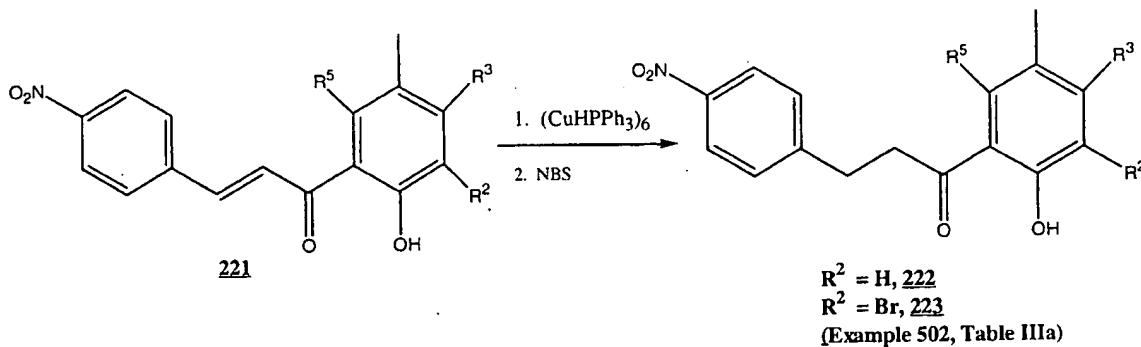
NBS (240 mmol) is added to a methanol solution of 2'-hydroxy-1-benzyl acetophenone (10 mmol) at 0°C. The 20 reaction is warmed to ambient temperature and stirred for 12 hours followed by dilution with water to yield a precipitate. The precipitate is isolated and dried under reduced pressure to yield 3.1 g of the title compound 503.

¹H NMR: (CDCl_3) δ ppm: 13.0 (s, 1H), 7.85 (s, 1H), 7.82 (s, 1H), 7.4-7.2 (m, 5H), 3.4 (t, 2H), 3.2 (t, 2H).

Example 515, Table IIIa

The title compound 515 is prepared by bromination of 2'-hydroxy-1-methyl acetophenone using the procedure for 30 503, above.

Scheme LV

**Example 502, Table IIIa (Scheme LV)**

5 **221** is prepared by the condensation procedure described in Scheme L1 above.

222 is prepared by the procedure discussed below:

10 In a 100 mL round bottom flask and under a nitrogen atmosphere, anhydrous benzene (20 mL) is added to **221** (2.5 g, 0.009 mol). To this solution is added $(\text{CuHPPPh}_3)_6$ (7.0 g, 0.0035 mol). The reaction mixture is stirred at ambient temperature for 1 hr, stirred open to the atmosphere 15 vigorously for 30 min, filtered through a pad of silica and eluted with 20% EtOAc/Hex. The filtrate is reduced and the residue purified by column chromatography on SiO_2 , with 20%Et₂O/hex as the eluent to give **222** as a yellow solid: 1.4 g, 0.0049 mol, 55%. MS (ESI) Calc for $\text{C}_{16}\text{H}_{15}\text{NO}_4$: 285.10, 20 Found: MH⁺ 286.0.

25 ¹H NMR (300 MHz, DMSO-d₆) δ : 11.58 (s, 1 H), 8.14 (d, 2 H, J = 7.6 Hz), 7.73 (s, 1 H), 7.59 (d, 2 H, J = 7.6 Hz), 7.31 (d, 1 H, J = 9.3 Hz), 6.86 (d, 1 H, J = 9.3 Hz), 3.47 (t, 2 H, J = 8.3 Hz), 3.1 (t, 2 H, J = 8.3 Hz), 2.27 (s, 3 H).

The title compound **223**, wherein R² = Br, is prepared by brominating **222** by the procedure in Scheme LII above.

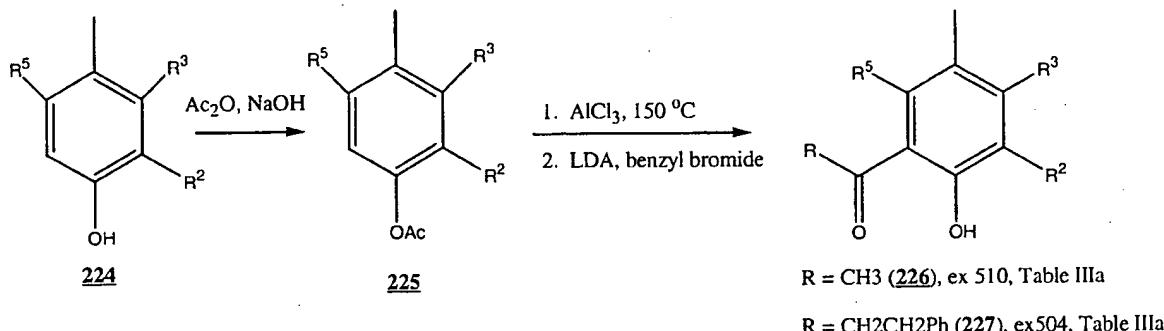
MS (ESI) Calc for $\text{C}_{16}\text{H}_{15}\text{NO}_4\text{Br}$: 363.03, Found: MH⁺ 363.6.

¹H NMR (300 MHz, DMSO) δ: 12.49 (s, 1 H), 8.17 (d, 2 H, J=9.4 Hz), 7.81 (s, 1 H), 7.72 (s, 1 H), 7.60 (d, 2 H, J = 9.4 Hz), 3.57 (t, 2 H, J = 8.2 Hz), 3.09 (t, 2 H, J = 8.2 Hz), 2.27 (s, 3 H).

5

Example 510, Table IIIa: General procedure for acetylation at the 2-position of phenols:

Scheme LVI



10

15 Ac_2O (60 mmol) is slowly added to a solution of water (30 ml), NaOH (60 mmol) and the phenol (**224**, 50 mmol) at 0°C . The reaction mixture is stirred for 10 min and then extracted with diethyl ether. The ether layer is washed with water, dried (MgSO_4) and concentrated to yield 9.6 g of the aryl acetate **225**.

20 ^1H NMR: (CDCl_3) δ ppm: 7.26 (br.s, 1H), 7.08 (br.d, 1H, J=8.2 Hz), 7.02 (d, 1H, J= 8.21 Hz), 2.38 (s, 3H), 2.37 (s, 3H).

25 The aryl acetate (**225**) and AlCl_3 (20 mmol each) were heated for 2 hours at 150°C . The reaction mixture is then diluted with HCl and water to yield the **226**. The product is filtered and dried under reduced pressure.

^1H NMR: (CDCl_3) δ ppm: 12.7 (s, 1H), 7.47 (br.s, 1H), 7.42 (br.s, 1H), 2.65 (s, 3H), 2.35 (s, 3H).

Example 521, Table IIIa: The title compound is prepared from 2'-hydroxy-3'-chloro acetophenone by alkylation with benzyl bromide using the procedure described for ex. 517, Table IIIa.

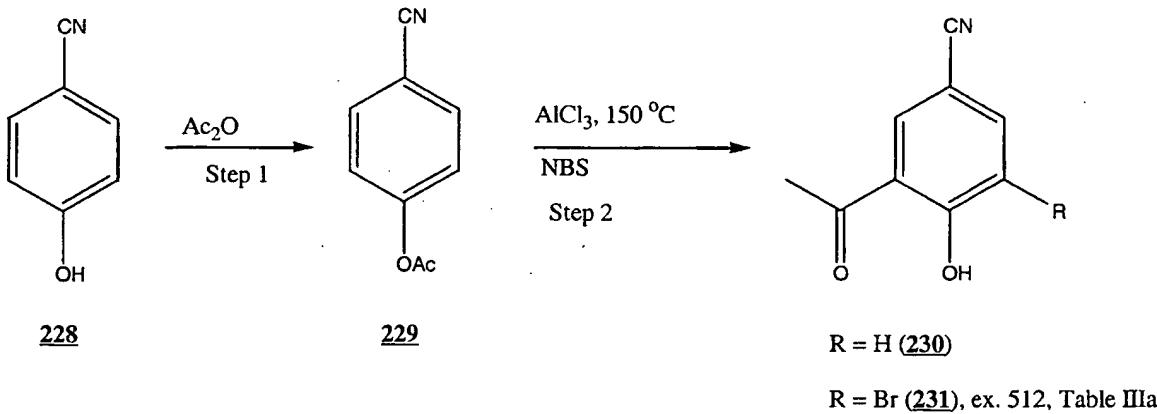
5

Example 513, Table IIIa: The title compound is prepared from ex. 525 by alkylation with benzyl bromide using the procedure described for ex. 517, Table IIIa.

Example 504, Table IIIa: The title compound is prepared from ex. 510 by alkylation with benzyl bromide using the procedure described for ex. 517, Table IIIa.

Example 512, Table IIIa: The title compound is prepared from 4-cyano phenol as shown in Scheme LVII below:

Scheme LVII



20 Step 1 and 2 are as described in Scheme LVI above. Step 3
is as described in Scheme LII above.

229: ^1H NMR: (CDCl_3) δ ppm: 7.7 (d, 2H, $J = 8.77$ Hz), 7.3 (d, 4H, $J = 8.80$ Hz).

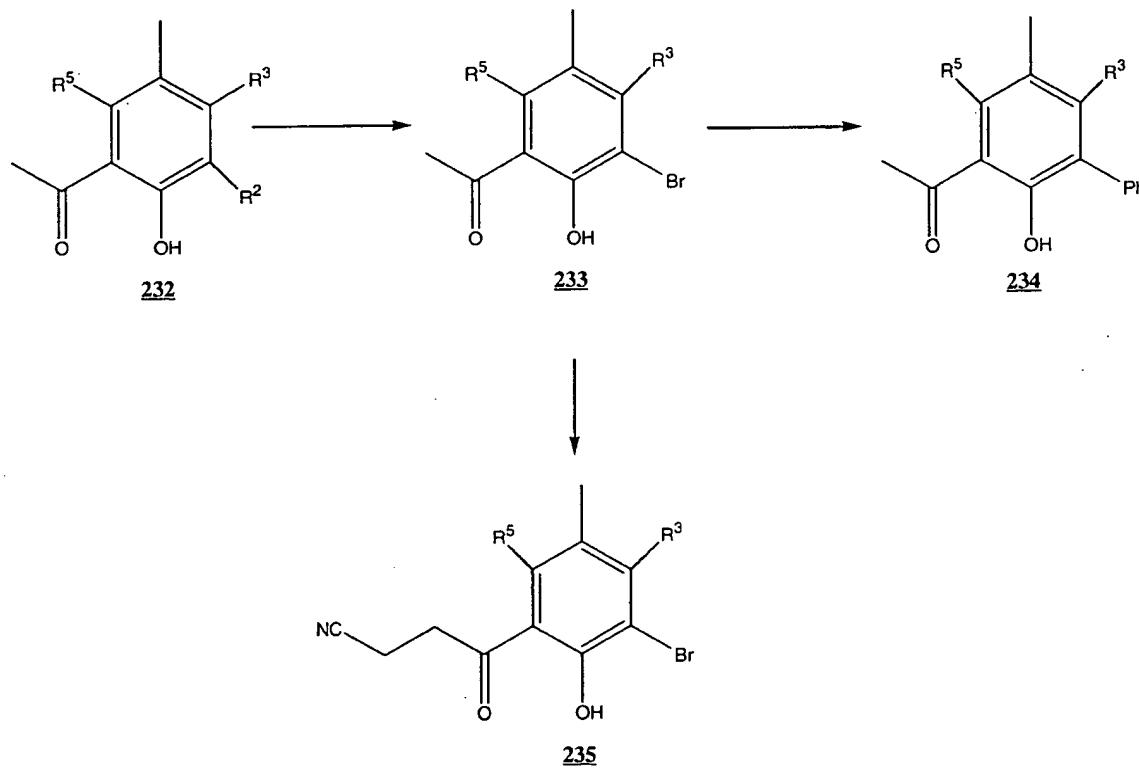
230: ^1H NMR: (CDCl_3) δ ppm: 12.7 (s, 1H), 8.15 (d, 1H, $J = 2.0$ Hz), 7.78 (dd, 1H, $J = 8.74$ Hz), 7.15 (d, 1H, $J = 8.66$ Hz), 2.7 (s, 3H).

231: ^1H NMR: (CDCl_3) δ ppm: 7.9 (br.s, 2H), 2.45 (s, 3H).

Example 507, Table IIIa: N-chloro succinimide (NCS) (12mmol) and 1-benzyl-2'-hydroxy acetophenone (10 mmol) are heated at 70° in methanol for two weeks. The mixture is then extracted with ether, and washed with water and concentrated to yield the title compound (1.8 g). The product is purified by flash chromatography on silica column using 1:3 diethyl ether : hexanes mixture.

10

Scheme LVIII



15

Scheme LVIII is a method that involves using a Suzuki coupling to generate substituted acetophenones (Example 519, Table IIIa).

The compound 2'-Hydroxy-3'-bromo-5'methylacetophenone 233 (Example 509, Table IIIa) is synthesized from the acetophenone using the bromination procedure in Scheme LII.

¹H NMR (DMSO-d₆) δ: 7.78 (d, 1 H) 7.70 (d, 1 H) 2.64 (s, 3 H) 2.26 (s, 3 H).

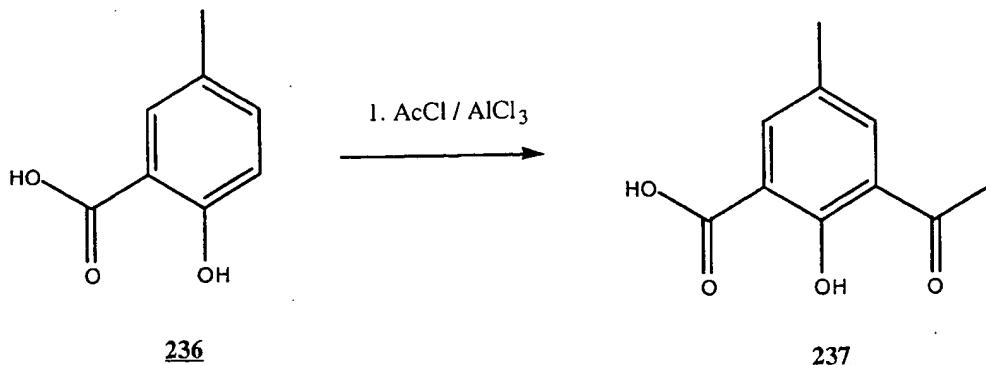
2'-Hydroxy-3'-bromo-5'methylacetophenone 233 (0.46 g, 2 mmol) and phenylboronic acid (0.24 g, 1 eq.) are dissolved in DME (10 ml) and placed under a nitrogen atmosphere. Na₂CO₃ (0.50 g, 3 eq.) in water (10 ml) is added, followed by Pd(Ph)₄ (0.12 g, 0.05 eq.) and the reaction mixture heated to 75°C for 12-18 h. Most of the DME is removed in vacuo and the reaction mixture is diluted with ether, washed with water, brine, and dried (MgSO₄), and concentrated in vacuo to give an oil. Purification by flash chromatography (5/95 EtOAc/hexanes) afforded 2'-Hydroxy-3'-phenyl-5'methylacetophenone 234 as a yellow solid (0.32 g, 71% yield) (Example 519, Table IIIa).

¹H NMR (DMSO-d₆) δ: 7.79 (d, 1 H) 7.53 (dd, 2 H) 7.46-7.30 (m, 4 H) 2.70 (s, 3 H) 2.33 (s, 3 H).

Alternatively 2'-Hydroxy-3'-bromo-5'methylacetophenone 233 can be treated as follows: LDA (20 mL, 1.5 M) is slowly added to a THF solution of 233 at about 0° and the reaction mixture is then cooled to about -78° followed by the addition of bromo acetonitrile (40 mmol). This resulting reaction mixture is stirred for 12-18 h at -78° and is then quenched with 1N HCl followed by extraction with ether. The ether layer is washed with water, dried (MgSO₄) and concentrated to yield an oil. This oil is purified by flash chromatography (4:1; hexanes:ethyl acetate) to yield 1 g of 235. (Example 517, Table IIIa)

¹H NMR (CDCl₃) δ ppm: 12.3 (s, 1H), 7.65 (s, 1H), 7.5 9s, 1H), 3.45 (t, 2H, J=7.14 Hz), 2.8 (t, 2H, J=7.3 Hz), 2.33 (s, 3H).

Scheme LVIX

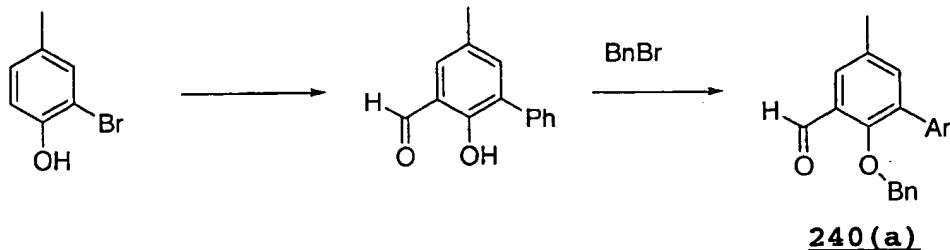


Acetyl chloride (14.7 ml, 5 eq.) is added slowly to an ice cooled suspension of AlCl₃ (27.7 g, 5 eq.) in dry CH₂Cl₂ (125 ml). The reaction is stirred until most of the solid is dissolved, then 5-methyl salicylic acid **236** (6.31 g, 41 mmol) is added. The reaction is stirred at 0°C for 1.5 hr, then at room temperature for 1.5 hr. The reaction is poured onto ice, diluted with Et₂O, and washed with water, brine, dried (MgSO₄). Concentration *in vacuo* afforded a slowly crystallizing oil. Recrystallization (CH₂Cl₂/hexanes) yielded pure 3-Acetyl-5-methyl salicylic acid (Example 529, Table IIIa) as 3.29 g of off white powder (41% recrystallized yield).

15 ¹H NMR (CDCl₃) δ: 8.22 (d, J = 1.88, 1 H) 7.80 (d, J = 1.98, 1 H).

Aldehyde compounds useful in the synthesis of Indole based compounds of Formula I are commercially available. They can also be prepared by schemes LX(1) to LX(5) outlined below.

Scheme LX(1)



2-Hydroxy-5-methyl-biphenyl-3-carbaldehyde 240(a)

The above compound is prepared as outlined and
5 discussed below:

3-Bromo-2-hydroxy-5-methylbenzaldehyde.

A mixture of 2-bromo-4-methylphenol (5.0 g, 27 mmoles), chloroform (50 ml), water (10 ml) and NaOH (10 g) was
10 refluxed for 3 hrs. The reaction mixture was cooled to ambient temperature, and then was acidified to pH = 2 with conc. HCl, diluted with ether (300 ml) and washed with 1N HCl (200 ml). The organic layer was dried (MgSO₄), filtered and concentrated to yield a residue which was purified using
15 flash chromatography (10% ethyl acetate/hexanes) to yield 2.94 g (51%) of the title compound as a light yellow solid.

2-Hydroxy-5-methyl-biphenyl-3-carbaldehyde

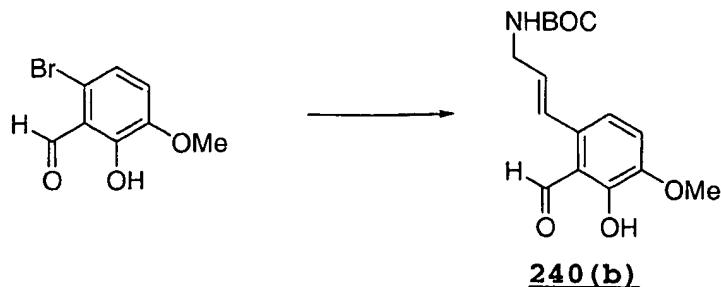
A mixture of 3-bromo-2-hydroxy-5-methylbenzaldehyde (0.30 g, 1.40 mmoles), phenyl boronic acid (0.20 g, 1.67 mmoles) and tetrakis(triphenylphosphine)palladium(0) (81 mg, 0.07 mmoles) in toluene (10 ml) and 2M K₂CO₃ (3 ml) was heated to 80 °C for 2 hr. The reaction mixture was cooled to ambient temperature, diluted with ether (100 ml) and washed with NaHCO₃. The organic layer was dried (MgSO₄), filtered and concentrated to yield a residue which was purified using flash chromatography (10% ethyl acetate/hexanes) to yield 0.15 g (49%) of the title compound as a yellow oil.

The yellow oil then was treated with Benzyl bromide
30 analogous to the procedure in Scheme VII above to yield the corresponding benzyl protected aldehyde.

Compounds analogous to 240(a) with different substituents can be prepared by following the procedure in Scheme LX(1) above.

35

Scheme LX(2)

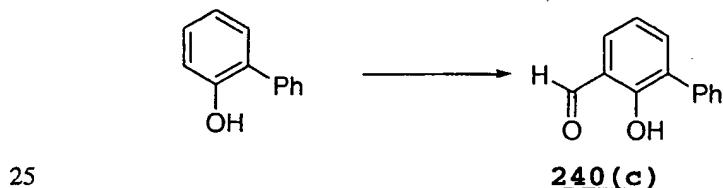


5 [3-(2-Formyl-3-hydroxy-4-methoxyphenyl)-prop-2-ynyl]-
carbamic acid *tert*-butyl ester. **240(b)**

A solution of 6-bromo-2-hydroxy-3-methoxybenzaldehyde (0.60 g, 2.6 mmoles) and prop-2-ynylcarbamic acid *tert*-butyl ester (0.44. 2.9 mmoles) in triethylamine (10 ml) was mixed
10 with tetrakis(triphenylphosphine)palladium(0) (60 mg, 0.05 mmoles) and copper iodide (15 mg, 0.08 mmoles). The reaction mixture was refluxed for 30 minutes, cooled to ambient temperature, diluted (ethyl acetate 200 ml) and washed with 0.5N HCl (50 ml). The organic layer was dried (MgSO₄),
15 filtered and concentrated to yield a residue which was purified by flash chromatography (30% ethyl acetate/hexanes) to yield 0.36 g (46%) of the title compound.

Compounds analogous to **240(b)** with different substituents can be prepared by following the procedure in
20 Scheme LX(2) above.

Scheme LX(3)



2-Hydroxy-biphenyl-3-carbaldehyde 240(c)

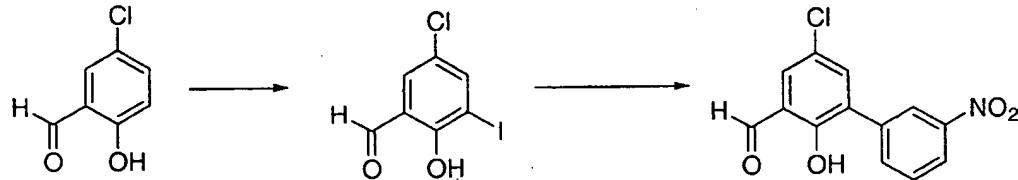
A solution of 2-Phenylphenol (300 mmol, 51 gr) and THF (400 mL) was mixed with triethylamine (3.5 eq, 145 ml) and
30 magnesium dichloride (1.5 eq, 43 gm.). The preceeding

mixture then was mixed with paraformaldehyde (6.0 eq, 54 gr) in portions over 10 min. to avoid vigorous exotherm forming a yellow mixture. The yellow mixture then was refluxed gently for 1.5 hours. A Thin Layer Chromatography (TLC) indicated a clean conversion to the more hydrophobic desired product ($R_f = 0.44$, 20% EtOAc/Hexane) and complete consumption of the starting phenol. The reaction mixture was cooled in an ice bath and then diluted with 3N HCl to adjust the pH to about 5. The acidified mixture then was extracted with ether or ethyl acetate, the combined organic layers were washed with water, brine, and dried (Na_2SO_4). The dried organic phase was concentrated to yield the title compound as an oil (54.6 gm., 92%).

HPLC , 254 nm, r.t.=8.8 min, 1-90% MeCN/H₂O, 0.05%TFA).
 NMR (300Mhz, ¹H CDCl₃): δ 11.6 ppm (s, 1H), 10.0 (s, 1H), 7.7 to 6.9 (m, 7H).

Compounds analogous to 240(c) with different substituents can be prepared by following the procedure in Scheme LX(3) above.

Scheme LX(4)

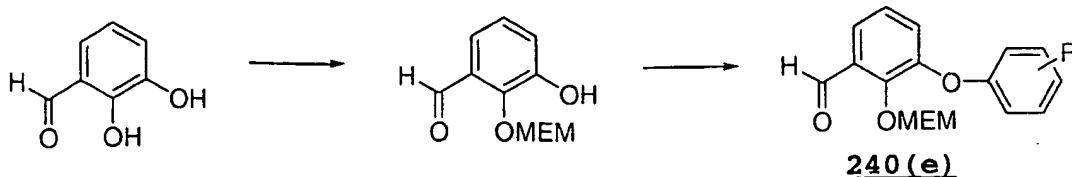


25

240(d)

The aldehyde 240(d) was prepared using the procedure outlined in Scheme X above. Compounds analogous to 240(d) with different substituents can be prepared by following the procedure in Scheme LX(4) above.

Scheme LX(5)

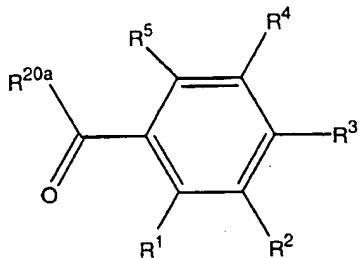


The 2,3-dihydroxy-benzaldehyde was treated with sodium hydride and MEM-chloride under conditions analogous to the benzylation procedure in Scheme VII to yield 250 mg, 1.1 mmol of the protected alcohol, which then was mixed with a DMF solution of Morpholino 4-chloro-3-nitro-benzenesulfoanamide (306 mg, 1 mmol) and the resulting mixture was heated for about 8-12 hours at about 80°C. The reaction mixture then was cooled to ambient temperature, diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate (2x) followed by brine (1x). The combined organic layers were dried over sodium sulfate, filtered and concentrated to yield a crude oily mixture. The crude was purified by passing through over silica gel eluting with 30% ethyl acetate in hexanes to give the product (120 mg) 24%.

Compounds analogous to 240(e) with different substituents can be prepared by following the procedure in Scheme LX(5) above.

Table IIIa lists ketones, that can be used as precursors to make compounds of Formula I, as illustrated in Scheme LXII for the general Fischer-Indole synthesis below. It should be noted that R^{20a} generally comprises an extra methylene group than R^2 , thus one can represent R^{20a} as CH_2-R^2 .

Table IIIa



wherein R¹ represents OH, and R⁵ represents H.

5

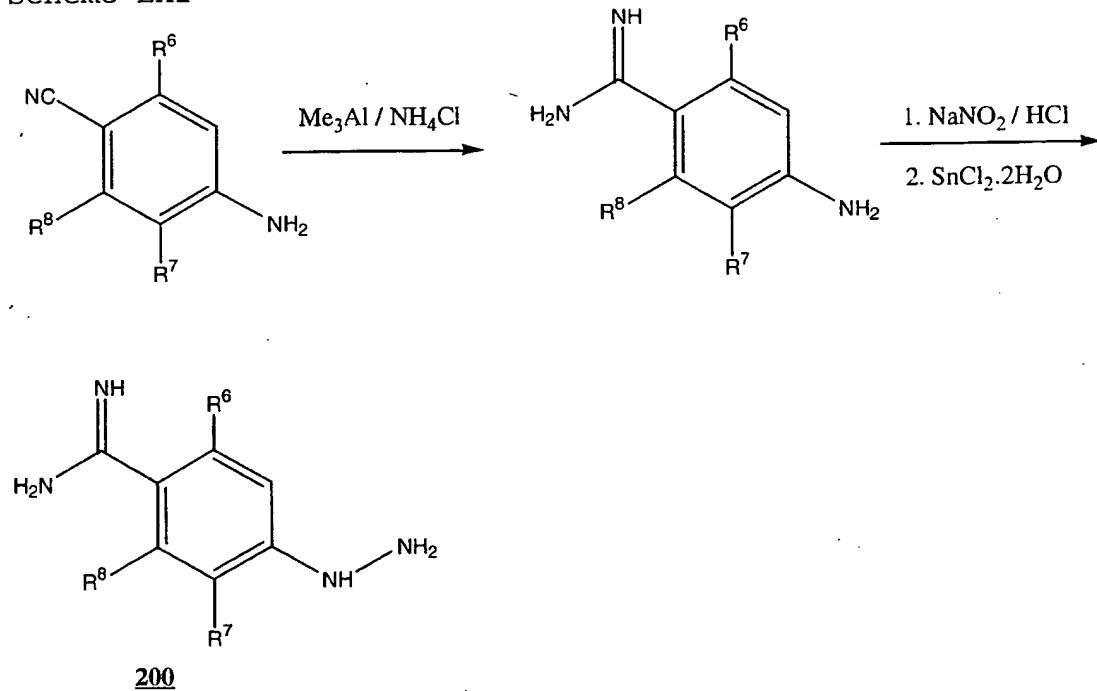
EX. No.	Sche me	R ²	R ³	R ⁴	R ^{20a}
500	LIII	Br	H	CH ₂ COO H	CH ₂ CH ₂ Ph
501	LII	Br	H	CH ₂ CH ₂ C OOH	CH ₂ CH ₂ Ph
502	LV	Br	H	CH ₃	CH ₂ CH ₂ (p- nitro)Ph
503		Br	H	Br	CH ₂ CH ₂ Ph
504	LVI	Cl	H	CH ₃	CH ₂ CH ₂ Ph
505	LI	F	H	F	CH ₂ CH ₂ Ph
506	LIII	Br	H	CH ₂ COO H	CH ₃
507		H	H	Cl	CH ₂ CH ₂ Ph
508	LIII	Br	H	CH ₂ CN	CH ₃
509	LVII I	Br	H	CH ₃	CH ₃
510	LVI	Cl	H	CH ₃	CH ₃
511	comm	Cl	H	Cl	CH ₃
512	LVII	Br	H	CN	CH ₃
513	LVII I	CH ₃	H	CH ₃	CH ₂ CH ₂ Ph

EX. No.	Sche me	R ²	R ³	R ⁴	R ^{20a}
514	comm	F	H	F	H
515		Br	H	Br	CH ₂ CH ₃
516	LVII I	3- thiophe ne	H	CH ₃	CH ₃
517	LVII I	Br	H	CH ₃	CH ₂ CH ₂ CN
518	comm	Br	H	Br	CH ₃
519	LVII I	Ph	H	CH ₃	CH ₃
520	LIV	Ph	H	H	CH ₃
521	LVII I	Cl	H	H	CH ₂ CH ₂ Ph
522		Br	H	nitro	CH ₃
523	comm	H	H	H	CH ₂ CH ₂ Ph
524	comm	H	H	Cl	CH ₃
525	LVI	CH ₃	H	CH ₃	CH ₃
526	LVII I	p- toluyl	H	CH ₃	CH ₃
527	comm	H	H	Br	CH ₃
528	comm	H	H	CH ₃	CH ₃
529	LVIX	COOH	H	CH ₃	CH ₃
530	comm	H	H	H	CH ₃
531	comm	H	H	H	CH ₂ CH ₃
532	LVII I	Br	H	CH ₃	CH ₂ CH ₂ Ph
533	comm	Cl	H	Cl	CH ₃
534	LV	Br	H	Me	CH ₂ CH ₂ (m- nitro)Ph
535	comm	OCH ₂ -R ³	OC H ₂ - R ²	H	CH ₃
535	comm	Cl	H	H	CH ₃

Synthesis of aryl hydrazines which are useful in the preparation of indole based compounds of Formula I in the Fischer-Indole synthesis discussed below.

5 Most of the aryl hydrazines are prepared using the procedure of Castro et al., J. med. Chem., 1994, Vol. 37, No. 19, p 3030 from commercially available materials. In the case of the chloro substituted hydrazine used in the synthesis of Example 839, Table III the following scheme is
10 used.

Scheme LXI

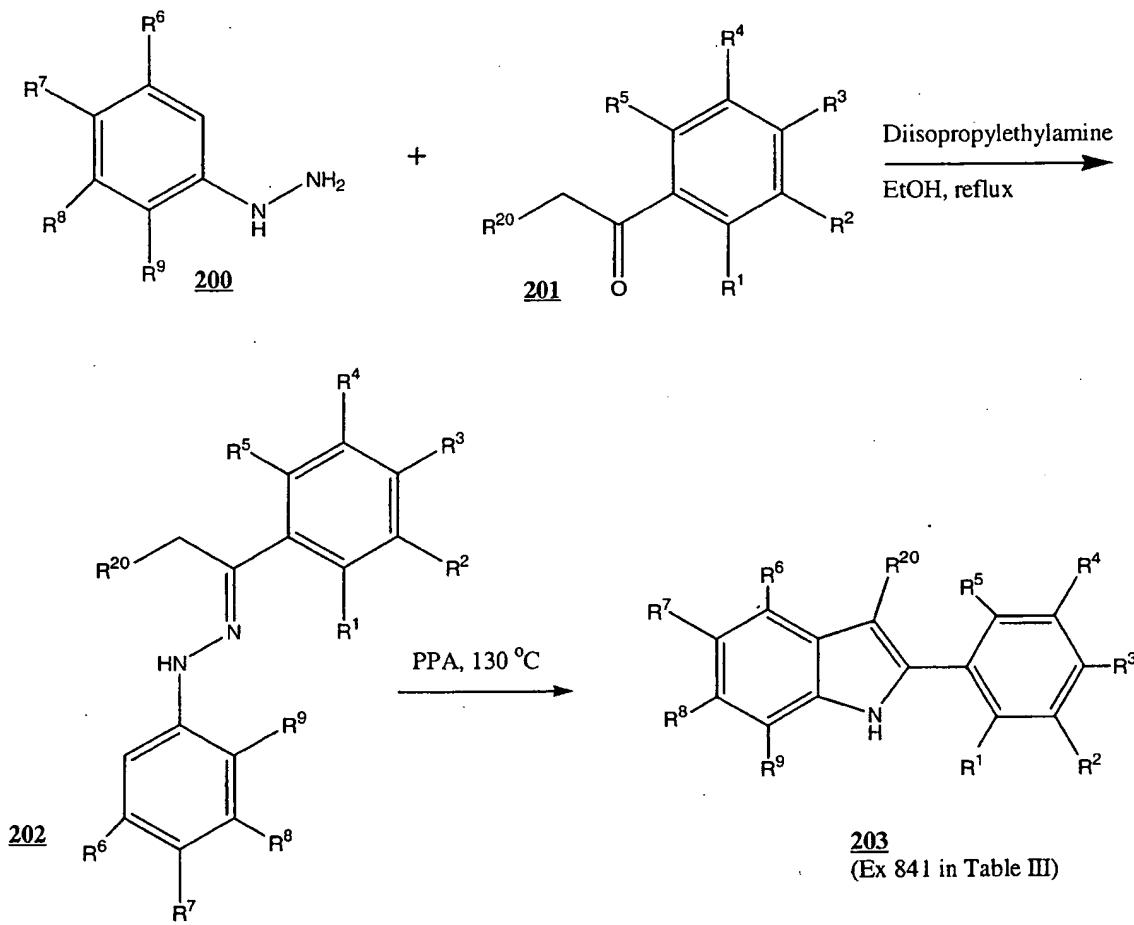


wherein R^8 is Cl; R^6 and R^9 are as defined in the detailed
15 description.

To a *p*-xylenes solution of the nitrile **255** (0.5 g, 3.3 mmol) is added a freshly prepared solution of $\text{Me}_3\text{Al}/\text{NH}_4\text{Cl}$ (16 ml, 3 eq.). ($\text{Me}_3\text{Al}/\text{NH}_4\text{Cl}$ solution can be prepared by adding 5g of ammonium chloride to *p*-xylenes (100ml) at 0°C, then adding a 2M solution of trimethylaluminum in toluene (48 ml) over 10 min. This mixture is stirred for 12-18 h as it is warmed up to ambient temperature. This mixture is
20

refluxed for 24 h, allowed to stand for 2 days and is then poured onto chloroform/silica gel. Filtration is followed by washing with 50% methanol/chloroform and then evaporation of the filtrates gives a yellow oil.
5 Purification is performed using reverse phase HPLC to give the amidine. This compound is then subjected to the same general procedure as noted above for the preparation of hydrazines from anilines.

10 General Fisher-Indole Synthesis of Indoles in Table III
Scheme LXII



15

Compounds of Formula in which 'A' is optionally substituted 1*H*-indol-2-yl and 'B' is optionally substituted

phenyl can be prepared by methods illustrated by Scheme LXII.

For example, a solution of 1-(3-bromo-2-hydroxy-5-methyl-phenyl)-3-(4-nitro-phenyl)-propan-1-one **201** (1.48 g, 0.004 mol), EtOH (30 mL), diisopropylethylamine (Hunigs base) (3 mL), and 4-Hydrazino-benzamidine **200** (0.93 g, 0.004 mol) is heated at reflux for 4 hr. (reaction times can vary between 2 h to 18 h). The solution is cooled to ambient temperature, filtered, washed with 6N HCl (2x25 mL), and dried for 12-18 h in a vacuum oven to give a 90% yield of 4-{N'-[1-(3-bromo-2-hydroxy-5-methyl-phenyl)-3-(4-nitro-phenyl)-propylidene]-hydrazino}-benzamidine **202** as an off-white solid (1.78 g, 0.0036 mol).

MS (ESI) Calc for $C_{23}H_{22}BrN_5O_3$: 495.1, Found: MH⁺ 496.1.

15

Example 841, Table III: A mixture of 4-{N'-[1-(3-bromo-2-hydroxy-5-methyl-phenyl)-3-(4-nitro-phenyl)-propylidene]-hydrazino}-benzamidine **202** (0.30 g, 0.0006 mol) and PPA (5 mL) was heated at 130°C (temperature may vary between 125 - 180 °C) for 30 min (reaction times may vary between 30 minutes - 4 h). The reaction mixture was cooled to ambient temperature and cold H₂O (5 mL) was added to produce a precipitate. The precipitate was washed and taken up in 0.1N HCl. Purification by reverse HPLC (0.01%HCl/acetonitrile) with a 2-90% gradient gave a 14% yield of 2-(3-bromo-2-hydroxy-5-methyl-phenyl)-3-(4-nitro-benzyl)-1H-indole-5-carboxamidine **203** as a white solid. (0.04 g, 0.08 mmol).

MS (ESI) Calc for $C_{23}H_{19}BrN_4O_3$: 478.08, Found: MH⁺ 479.4.

30

¹HNMR (300 MHz, DMSO-d₆) δ: 11.84 (s, 1 H), 9.24 (s, 1 H), 9.11 (s, 2 H), 8.70 (s, 2 H), 8.06 (d, 2 H, J = 7.6 Hz), 8.04 (s, 1 H), 7.60-7.56 (m, 2 H), 7.36 (s, 1 H), 7.34 (d, 2 H, J = 7.6 Hz), 6.03 (s, 1 H), 4.21 (s, 2 H), 2.20 (s, 3 H).

35

3-(4-amino-benzyl)-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine (Example 803, Table III):

A mixture of 2-(3-bromo-2-hydroxy-5-methyl-phenyl)-3-(4-nitro-benzyl)-1H-indole-5-carboxamidine **203** (100 mgs, 0.2 mmol), SnCl₂ (100 mgs) and 6N HCl is heated at reflux for 1 hr. The reaction is cooled, let stand for 12-18 h, 5 and the residue is isolated. The residue is taken up in 0.1N HCl and purified by reverse phase HPLC (0.01%HCl/acetonitrile) with a 2-90% gradient to yield 42% of 3-(4-amino-benzyl)-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine as a white solid (38 mgs, 10 0.08 mmol).

MS (ESI) Calc for C₂₃H₂₁BrN₄O: 448.11, Found: MH⁺ 448.9.

¹HNMR (300 MHz, DMSO) δ: 11.77 (s, 1 H), 9.24 (s, 1 H), 9.14 (s, 2 H), 8.75 (s, 2 H), 8.05 (s, 1 H), 7.56 - 7.52 (m, 2 H), 7.44 (s, 1 H), 7.04 - 7.15 (m, 5 H), 4.07 (s, 2 H), 2.2 (s, 3 H).

Alternative synthesis of Indoles

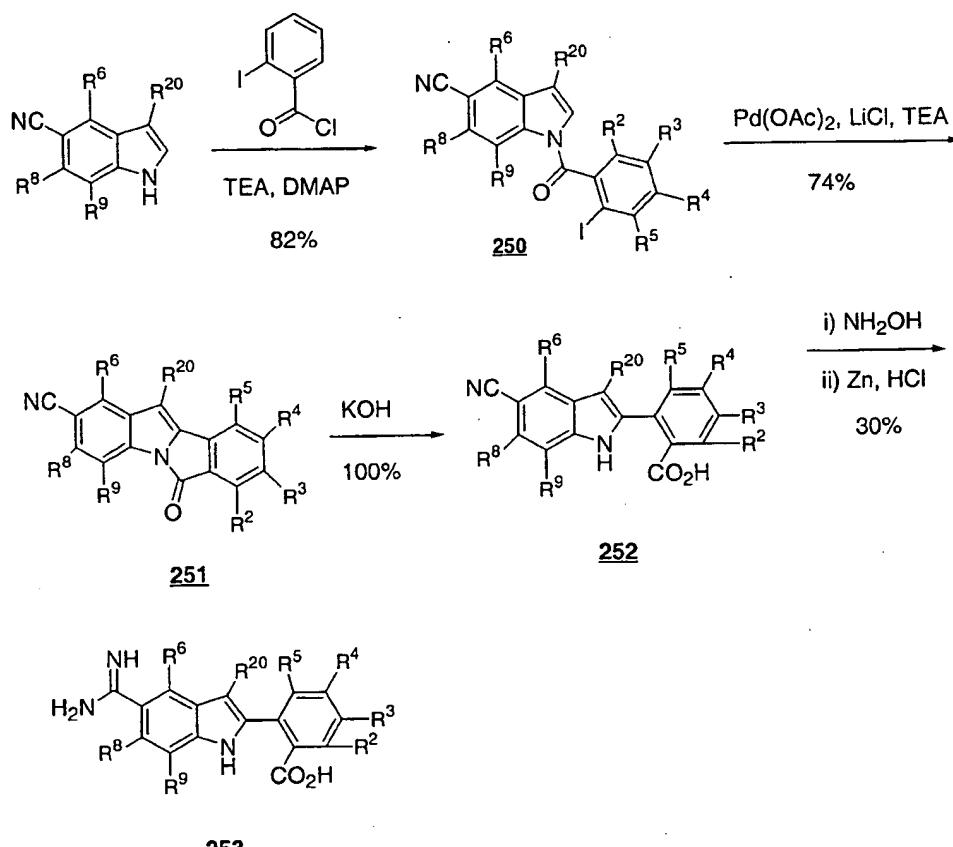
Compounds of Formula I having an indole nucleus can also be synthesized using the procedure discussed in Scheme 20 LXIII below.

25

30

35

Scheme LXIII



5 A solution of 2-iodo-benzoyl chloride (2.05 g, 7.7 mmol) in DCM (5.0 mL) is added over a period of 5 min to a stirring DCM solution containing 5-cyano-indole (1.0 g, 7.0 mmol), TEA (1.95 mL, 14 mmol), DMAP (100 mg, 0.8 mmol) at 10 0°C. The resulting solution is stirred for an additional 1 hz at ambient temperature. The reaction mixture is then diluted with DCM (50 mL) and washed with H₂O (x3), and sat. NaHCO₃ (x3). The organics were then dried (Na₂SO₄), and concentrated in vacuo. The residue is recrystallized 15 (EtOAc/Hexanes) to provide 2.14 g (82%) of 5-cyano-1-(2-iodo(carboxyphenyl))indole **250** as a white solid.

¹H-NMR (300 MHz, CDCl₃) δ: 8.56 (d, 1H, J = 4.5 Hz), 8.01 (d, 1H, J = 8.1 Hz), 7.91 (s, 1H), 7.71 (d, 1H, J = 8.1 Hz), 7.60 (t, 1H, J = 7.5 Hz), 7.50 (d, 1H, J = 7.5 Hz), 7.34

(t, 1H, J = 7.8 Hz), 7.14 (d, 1H, J = 3.6 Hz), 6.73 (d, 1H, J = 3.6 Hz). MS (+CI, CH₄); m/z 373 (MH⁺), 245, 143.

A mixture of 5-cyano-1-(2-iodo(carboxyphenyl))indole **250** (1.0g, 2.6mmol), Pd(OAc)₂ (59 mg, 0.26 mmol), triphenylphosphine (120 mg, 0.52 mmol), Et₃N (0.73 mL, 5.2 mmol), and LiCl (120 mg, 2.8 mmol), in CH₃CN (20 mL) is refluxed under N₂ for 18 h. Upon cooling, **251** crystallizes out as yellow/green needles.

¹H-NMR (300 MHz, DMSO-d₆) δ: 8.07 (s, 1H), 7.84 (d, 2H, J = 8.1 Hz), 7.76 (d, 1H, J = 7.2 Hz), 7.67 (t, 2H, J = 7.2 Hz), 7.47 (t, 1H, J = 7.5 Hz), 7.02 (s, 1H).

MS (+CI, CH₄); m/z 245 (MH⁺), 143.

Compound **251** (74 mg, 0.2 mmol) in MeOH (1.0 mL) is treated with KOH (1.0 mL, 40% aq) and heated to 60 °C for 30 min. The mixture is then cooled to ambient temperature and diluted with H₂O (10 mL). The aqueous solution is then acidified with HCl (6 N) to pH = 2.0. The resulting solid precipitate is isolated, washed with H₂O, and dried in vacuo to provide 70 mg of **252** (90%) as a white solid.

¹H-NMR (300 MHz, DMSO-d₆) δ: 8.05 (s, 1H), 7.80 (d, 1H), 7.65 (m, 2H), 7.55 (m, 2H), 7.44 (d, 1H), 6.65 (s, 1H). MS (Bioion) m/z 261.6 (MH⁺), 168.9.

Compound **252** (35 mg, 0.13 mmol) in EtOH (2.0 mL) is treated with NH₂OH (66 uL, 1.0 mmol, of a 50% soln. in H₂O) and refluxed for 16 h. The reaction mixture is concentrated in vacuo, and the residue is taken up in EtOH (4 mL). The ethanol solution is then treated with HCl (1.0 mL of a 4 N soln. in Dioxane) and heated to 60 °C. At this point Zn dust (65 mg, 1.0 mmol) is added and the reaction mixture is allowed to stir for 16 h at 60 °C. The resulting solution is then cooled and filtered. The filtrate is concentrated and purified by HPLC (C₁₈; H₂O/CH₃CN) to provide 15 mg (35%) of **253** (Example 836, Table III) as a white powder.

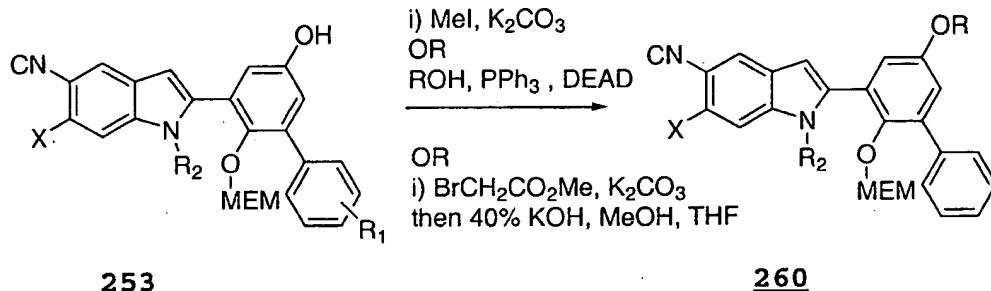
¹H-NMR (300 MHz, DMSO-d₆) δ: 11.99 (s, 1H), 9.18 (s, 2H), 8.80 (s, 2H), 8.12 (s, 1H), 7.77 (d, 1H), 7.63 (m, 2H), 7.53 (m, 3H), 6.67 (s, 1H).

MS (+ESI): calcd. for C₁₆H₁₄N₃O₂; Found: m/z 280.1 (MH⁺).

Compounds 253 where R¹ represents a protected hydroxy group or other appropriate R¹ substituents and R⁴ represents OH can be derivatised at the R⁴ position by converting the hydroxy group to an alkyl hydroxy group with or without a functional group, as indicated in Scheme LXX below:

Scheme LXX

10



[5-(6-Chloro-5-cyano-1-methansulfonyl-1*H*-indol-2-yl)-6-(2-methoxyethoxymethoxy)biphenyl-3-yloxy]acetic acid ethyl ester 260

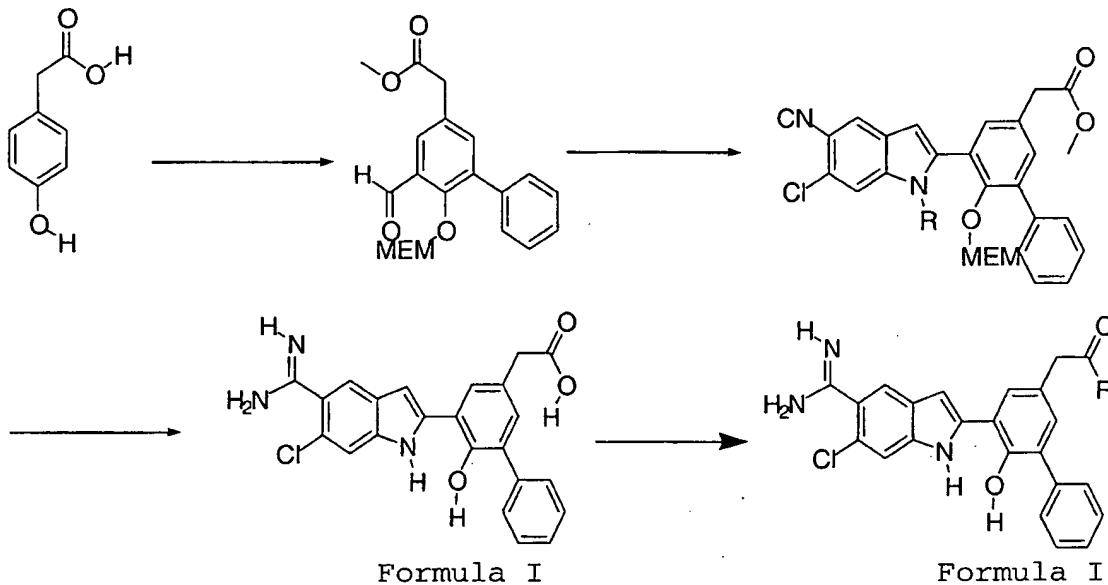
A mixture of 6-chloro-2-[5-hydroxy-2-(2-methoxyethoxymethoxy)biphenyl-3-yl]-1-methansulfonyl-1*H*-indole-5-carbonitrile (7.0 g, 13 mmoles) and K₂CO₃ (5.5 g, 23 mmoles) in acetonitrile (200 ml), was mixed with NaI (0.5 g) and bromoethyl acetate (1.6 ml, 14 mmoles). The mixture was stirred for about 18 h at ambient temperature, concentrated, the residue was dissolved in ethyl acetate (400 ml) and washed with brine. The organic layer was dried (MgSO₄), filtered and concentrated to afford 8.0 g (98%) of the title compound as a brown foam.

Removal of protecting mesyl group at teh R¹ position was accomplished by mehtods known to one skilled in the art. Compounds where R⁴ represent a substituent comprising a carboxylic acid group can be converted to corresponding amides using the procedures outlined in of Scheme C above.

Compounds of Formula I wherein R⁸ represents a halo group can be synthesized as outlined in Scheme LXXI below:

Scheme LXXI

5



10 (4-Hydroxy-phenyl)-acetic acid methyl ester

4-Hydroxyphenylacetic acid (126 mmol, 19.2g) was dissolved in MeOH (400 ml) and the resulting mixture was cooled in an ice bath (0° C) under N₂ atmosphere. The 15 cooled reaction mixture was saturated with HCl (gas) and the reaction mixture then was refluxed for 2 h or until all the starting material was completely consumed. The reactin mixture was concentrated and the resulting residue was dissolved in ether, washed with water, brine, dried (Na₂SO₄) and concentrated to yield a light colored oil (24.7 g). The 20 purity of this crude material was 95% by HPLC and underwent no further purification prior to the next step.

HPLC (254 nm, r.t.= 7.1 min., 1-90% MeCN/H₂O, 0.05% TFA)
25 NMR (¹H-300MHz, DMSO-d₆): δ 7.1 (d, 2H), 6.7 (d, 2H), 6.0 (bs, 1H), 3.7 (s, 3H), 3.5 (s, 2H).

(3-Formyl-4-hydroxy-phenyl)-acetic acid methyl ester (3)

The methyl ester from above (126 mmol, 21g) was dissolved in acetonitrile (650 mL) to form a solution. This
5 solution was mixed with triethylamine (3.4 eq, 60 ml), magnesium dichloride (1.6 eq, 19.7 g), paraformaldehyde in several portions (6.8 eq, 26 gr) to form a yellow mixture. The yellow mixture was refluxed for 3.5 hours at which time TLC revealed that all the starting material was consumed.
10 The reaction mixture was acidified with 6 N HCl, concentrated and extracted with ether (3x150 ml). The ether extracts were washed with water, brine, dried (Na_2SO_4) and concentrated to yield 23.6g (96%) of crude product.

15 NMR (^1H , DMSO- d_6): δ 10.6 (s, 1H), 10.4 (s, 1H), 7.5 (s, 1H), 7.4 (d, 1H), 6.9 (d, 1H), 3.62 (s, 2H), 3.59 (s, 3H).

(3-Bromo-5-formyl-4hydroxy-phenyl)-acetic acid methyl ester (4)

20 The salicylaldehyde from above (122 mmol, 23.6 g) was dissolved in 120 ml acetic acid. Bromine (1.9 eq, 12 ml) was added drop wise over 30 minutes and the dark solution stirred overnight under N_2 . Volatiles were removed under reduced pressure, the residue dissolved in ether, washed with water followed by brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield an oil (32.2 g) (97%).
25

30 NMR (^1H , DMSO) : δ 11.1(bs, 1H), 10 (s, 1H), 7.8 (s, 1H), 7.6 (s, 1H), 3.7 (s, 2H), 3.6 (s, 3H).

[3-Bromo-5-formyl-4-(2-methoxy-ethoxymethoxy)-phenyl]-acetic acid methyl ester (5)

35 A solution of the aryl bromide (4) (118 mmol, 32.2 g) was dissolved in chloroform (550 mL) was mixed with DIPEA

(2.35 eq, 48 ml) followed by rapid drop wise addition of MEM-Cl (2-Methoxy-ethoxymethyl chloride, 1.19 eq, 16 ml). The resulting reaciton mixture was stirred for 8-12 h. The reaction mixture was concentrated, and diluted with ether.

5 The ether mixture was washed with 0.5 M KHSO₄, followed by saturated NaHCO₃, and brine. The organic phase was dried (Na₂SO₄) and concentrated to give a crude oil (43.2g) 91% pure by HPLC, no further purification performed.

10 HPLC 254 nm, r.t. = 8.0 min., 1-90% MeCN/H₂O, 0.05% TFA). NMR (¹H, CDCl₃): δ 10.3 (s, 1H), 7.8 (s, 1H), 7.7 (s, 1H), 5.3 (s, 2H), 3.9 (d, 2H), 3.65 (s, 2H), 3.5 (d, 2H), 3.4 (s, 3H).

15 [5-formyl-6-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetic acid methyl ester (6)

The arylbromide (5) (118 mmol, 42.6 gr) was dissolved in about 430 ml of toluene in a 1 L flask to which 150 ml of 20 2M K₂CO₃ was added followed by 5.0 g (0.037 eq) of Pd(PPh₃)₄. After the addition of phenylboronic acid (2.0 eq, 29 gr) the flask was heated to 70°C and the mixture stirred for 5 hours. HPLC of the reaction mixture indicated that the arylbromide had completely reacted and a dominant less polar moiety 25 (89% pure, r.t.= 8.5 min., 1-90% MeCN/H₂O, 0.1% TFA) was observed.

The organic layer from the reaction mixture was isolated, concentrated and diluted with ether. The ether mixture was washed with water, brine and dried with Na₂SO₄. The 30 resulting organic layer was concentrated and the residue obtained was purified by silica gel column, 30% EtOAc/Hexane to yield 23.7g, 66% of the title compound.

NMR (¹H, DMSO-d₆): δ 10.3 (s, 1H), 7.65 (s, 1H), 7.59 (s, 1H), 7.5-7.3 (m, 5H), 4.8 (s, 2H), 3.8 (s, 2H), 3.6 (s, 2H), 3.4 (d, 2H), 3.2 (d, 2H), 3.1 (s, 3H).

MS: (ESI ,Sciex) m/z = 357.4

[5-(6-Chloro-5-cyano-1-methanesulfonyl-1H-indol-2-yl)-6-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetic acid methyl ester (15)

5

See general Scheme X using the above aldehyde 6

NMR (^1H , DMSO-d₆): δ 8.4 (s, 1H), 8.2 (s, 1H), 7.6-7.3 (m, 7H), 6.9 (s, 1H), 4.6 (s, 2H), 3.7 (s, 3H), 3.65 (s, 2H), 10 3.25 (s, 2H), 3.2 (s, 3H), 3.0 (b, 1H).

MS: (ESI, Sciex): m/z = 579

[5-(6-Chloro-5-cyano-1-methanesulfonyl-1H-indol-2-yl)-6-hydroxy- biphenyl-3-yl]-acetic acid methyl ester (16)

15

The indole (15) was dissolved in 80 ml methanol treated with 80 ml of 4 N HCl/dioxane at ambient temperature for about 2h. TLC analysis indicated that all the starting material was consumed and a new product had formed (R_f = 20 0.30, 40% EtOAc/ Hexane). Volatiles were removed by rotary evaporation, the residue was dissolved in ethyl acetate which was washed three times with water followed by brine. After drying with Na₂SO₄, concentration gave a crude residue of 3.8g, 84% pure by HPLC (254 nm).

25

NMR (^1H , DMSO-d₆): δ 8.2 (s, 1H), 7.9 (s, 1H), 7.6-7.4 (m, 7H), 7.3 (s, 1H), 6.7 (s, 1H), 3.7 (s, 3H), 3.6 (s, 2H), 3.3 (s, 3H).

MS: (ESI, Sciex): M = 495.

30

[5-(6-Chloro-5-cyano-1H-indol-2-yl)-6-hydroxy-biphenyl-3-yl]-acetic acid (17)

The phenol (16) (4.3g, 8.7 mmol) was dissolved in 40 35 ml methanol and 15 ml water. To this was added 32 ml of 14 N NaOH (aq) and the solution was stirred for two hours at ambient temperature. HPLC indicated that all the starting

material was consumed and a new moiety had formed. The reaction mixture was diluted water (50 mL), acidified with 6 N HCl and extracted with EtOAC. The organic layer was washed with water (2x), brine and then dried (Na_2SO_4) and concentrated to yield a yellow solid, 3.0g, 87%.

HPLC r.t. = 7.5 min. (1-90% MeCN/H₂O, 0.05% TFA) .

MS: (ESI, Sciex): m/z = 403.2 (MH⁺)

10 {5-[6-Chloro-5-(N-hydroxycarbamimidoyl)-1H-indol-2-yl]-6-
hydroxy-biphenyl-3-yl}-acetic acid (18)

A solution of the cyano indole (17) (0.365 gr, 0.91 mmol) from above in dry EtOH (5 ml) was treated with an excess of Hydroxylamine (5 ml of 50 wt. % solution in water). The resulting reaction mixture was refluxed for 10h. The solvent was removed by rotary evaporation, the residue was azeotroped with toluene to yield the title compound (0.3-0.4g).

20

HPLC r.t. = 6.7 min., 1-90% MeCN/H₂O, 0.05% TFA) .

MS: (ESI, Sciex): m/z= 436 (MH⁺)

25 [5-(5-Carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-
biphenyl-3-yl]-acetic acid (19)

Acetic anhydride (1.1 eq, 0.77ml, in 7 ml of AcOH) was added drop wise to a stirring solution of 3g of 18 in 34 ml of acetic acid at ambient temperature under N₂ over several minutes. HPLC 15 minutes thereafter indicated formation of a hydrophobic product. A catalytic amount of Pd/C (10% w/w) was added to the reaction mixture and the reaction vessel then was charged with H₂ (atm.). The reaction mixture was agitated for about 1.5h. The agitated reaction mixture was passed through a celite pad (rinsed with AcOH). The filtrate was diluted with ethyl acetate to yield a

precipitate. The solid was isolated and dried in vacuo to yield 2.05g of the crude amdidine.

MS: (ESI, Sciex): m/z= 419

5

2-[5-(5-Carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxybiphenyl-3-yl]-N,N-dimethyl-acetamide

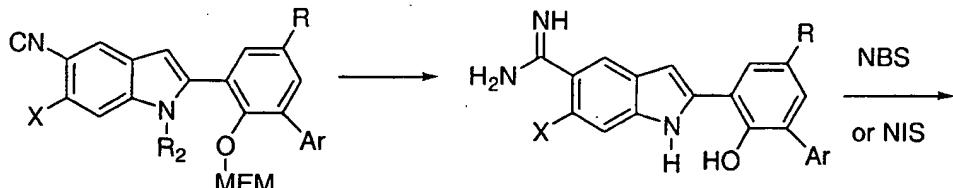
The compound (**19**) from above (87 mg, 0.18 mmol) was combined with dimethylamine HCl (82 mg, 1.9 eq), EDC (425 mg, 1.2 eq), HOBT_{H2O} (300 mg, 1.2 eq) and DIPEA (0.45 ml, 1.4 eq) in 15 ml DMF. The reaction mixture was stirred overnight. A new moiety was observed by HPLC which LC.MS.ESI (Sciex) confirmed as the product having a mass of 447 A solution of 9:1 EtOAc / ether was added to the reaction mixture to afford a precipitate. The precipitated solid was isolated and purified by preparative HPLC (2-90% MeCN/ H₂O in 40 min., 20 mM HCl) to yield the title compound (88 mg) (11% yield).

20

Another method to make compounds of Formula I listed in Table III is depicted in Scheme LXXIII below:

Scheme LXXIII

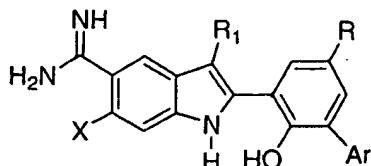
25



X= Cl or F, R₂ = Mes or BOC

260

263



264

30

6-Chloro-2-[2-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-1H-indole-5-carboxamidine 260

The cyano-indole was dissolved in 300 ml dry EtOH in a
5 1 L flask fitted with a drying tube. Twenty (20) equivalents
of hydroxylamine HCl (54g) and K₂CO₃ (107g) were added and the
mixture refluxed overnight. The product was observed by HPLC
as was a significant amount of the starting indole. An
10 additional 10 eq of both hydroxylamine HCl and K₂CO₃ were
added and the reaction mixture refluxed for an additional 8-
12h. HPLC indicated the reaction had progressed, with about
5% of the starting material remaining. The solid was
separated and the filtrate concentrated to yield residue.
The residue was diluted with ethyl acetate, washed with
15 water, the organic layer was dried (Na₂SO₄) and concentrated
under reduced pressure to yield compound 260.

LC.MS.ESI (Sciex) : m/z = 466

HPLC (r.t.= 7.46 min, 254 nm, 1-90% MeCN/H₂O, 0.05% TFA)

20

6-Chloro-2-[2-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-1H-indole-5-carboxamidine 262

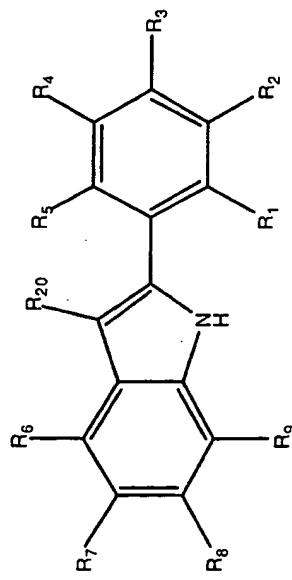
25 Compound 260 was dissolved in AcOH (50 ml) and diluted
with acetic anhydride. After about an hour the formation of
compound 262 was observed. The reduction of the acetylated
hydroxyamidine was performed *in situ* by addition of 2g
30 (0.05 eq) of Pd/C (palladium on activated carbon, 5% dry
weight) and charging the flask with H₂ (1 atm). After six
hours amidine formation was observed. The reaction mixture
was passed through a celite pad, the clear filtrate
concentrated to a residue which was purified by silica gel
column (5% MeOH/ 2.5% AcOH / DCM to 10% MeOH/ 5% AcOH /
35 DCM), the pure fractions concentrated to give 6.0 g (35%) of
product 263.

6-Chloro-2-(2-hydroxy-biphenyl-3-yl)-1H-indole-5-carboxamidine, 264

The product **263** (13.3 mmol) was dissolved in 50 ml of dry MeOH and 50 ml of anhydrous 4 M HCl/dioxane at r.t. under N₂. After agitating the reaction mixture for about an hour, the starting material was consumed and product formatin was observed by HPLC at r.t. = 7.25 min (254 nm, 1-90% MeCN/ H₂O, 0.05% TFA). The solvent was removed under reduced pressure, to yield a foamy oil. The foamy oil was diluted with 0.5 m HCl (aq) to from a precipitate. The precipitated solid was isolated and dried to yield the title compound (2.7 g).

15

Table III



EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R'	R ⁸	R ⁹	R ²⁰
801	OH	Br	H	CH ₂ COO H	H	H	C (=NH) NH ₂	H	H	benzyl
802	OH	Br	H	(CH ₂) ₂ COOH	H	H	C (=NH) NH ₂	H	H	benzyl
803	OH	Br	H	CH ₃	H	H	C (=NH) NH ₂	H	H	4-amino- benzyl
804	OH	Br	H	Br	H	H	C (=NH) NH ₂	H	H	benzyl
805	OH	C1	H	CH ₃	H	H	C (=NH) NH ₂	H	H	benzyl
806	OH	F	H	F	H	H	C (=NH) NH ₂	H	H	benzyl
807	OH	Br	H	CH ₂ COOH	H	H	C (=NH) NH ₂	H	H	H

EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R'	R ⁸	R ⁹	R ²⁰
808	OH	H	H	C1	H	H	C(=NH) NH ₂	H	H	benzyl
809	OH	Br	H	CH ₂ CON	H	H	C(=NH) NH ₂	H	H	H
810	OH	Br	H	CH ₃	H	H	C(=NH) NH ₂	H	H	H
811	OH	C1	H	CH ₃	H	H	C(=NH) NH ₂	H	H	H
812	OH	C1	H	C1	H	H	C(=NH) NH ₂	H	H	H
813	OH	Br	H	CONH ₂	H	H	C(=NH) NH ₂	H	H	H
814	OH	CH ₃	H	CH ₃	H	H	C(=NH) NH ₂	H	H	benzyl
815	OH	F	H	F	H	H	C(=NH) NH ₂	H	H	H
816	OH	Br	H	Br	H	H	C(=NH) NH ₂	H	H	CH ₃
817	OH	thiophe n-3-yl	H	CH ₃	H	H	C(=NH) NH ₂	H	H	H
818	OH	Br	H	CH ₃	H	H	C(=NH) NH ₂	H	H	CH ₂ CONH ₂
819	OH	Br	H	Br	H	H	C(=NH) NH ₂	H	H	H
820	OH	Ph	H	CH ₃	H	H	C(=NH) NH ₂	H	H	H
821	OH	Ph	H	H	H	H	C(=NH) NH ₂	H	H	H
822	OH	C1	H	H	H	H	C(=NH) NH ₂	H	H	benzyl
823	OH	Br	H	nitro	H	H	C(=NH) NH ₂	H	H	H
824	OH	H	H	H	H	H	C(=NH) NH ₂	H	H	benzyl
825	OH	H	C1	H	H	H	C(=NH) NH ₂	H	H	H

EX. NO.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R'	R ⁸	R ⁹	R ²⁰
826	OH	Br	H	CH ₃	H	C(=NH)NH ₂	H	H		CH ₂ COOH
827	OH	CH ₃	H	CH ₃	H	C(=NH)NH ₂	H	H		H
828	OH	p-toluyl	H	methyl 1	H	C(=NH)NH ₂	H	H		H
829	OH	H	H	Br	H	C(=NH)NH ₂	H	H		H
830	OH	H	H	methyl 1	H	C(=NH)NH ₂	H	H		H
831	OH	COOH	H	methyl 1	H	C(=NH)NH ₂	H	H		H
832	OH	H	H	H	H	C(=NH)NH ₂	H	H		H
833	OH	H	H	H	H	C(=NH)NH ₂	H	H		methyl
834	CO	OH	H	H	H	C(=NH)NH ₂	H	H		H
835	CO	Ethoxy	H	H	H	C(=NH)NH ₂	H	H		H
836	CO	OH	H	H	H	C(=NH)NH ₂	H	H		H
837	OH	Br	H	CH ₃	H	C(=NH)NH ₂	H	H		benzyl
838	OH	C1	H	C1	H	C1	C(=NH)NH ₂	H	H	H
839	OH	C1	H	C1	H	C(=NH)NH ₂	C1	H	H	H

EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰
840	OH	Ph	H	H	H	H	NHC(=NH)N H ₂	H	H	H
841	OH	Br	H	Me	H	H	C(=NH)NH ₂	H	H	p-nitrobenz y1
842	OH	Br	H	Me	H	H	C(=NH)NH ₂	H	H	m-nitrobenz y1
843	OH	O-CH ₂ -CH ₂ -O	H	H	H	H	C(=NH)NH ₂	H	H	H
844	H	H	4-Y ¹⁰ xybenzamidine	H	H	H	C(=NH)NH ₂	H	H	H
845	OH	Br	H	Me	H	H	H	C(=N H)NH	H	H
846	OH	Ph	CH ₂ C OOH	H	H	H	C(=NH)NH ₂	C1	H	H
847	OH	Ph	H	2-Piperidin-1-yl-ethylcarbamoyl)-methyl	H	H	C(=NH)NH ₂	C1	H	H

EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R'	R ⁸	R ⁹	R ²⁰
848	OH	Ph	H	Benzylcarb- amoyl- methyl- y1	H	H	C (=NH) NH ₂	C1	H	H
849	OH	Ph	H	Morpholin -2- -4-Y1- ethylicarb- amoyl)- methyl	H	H	C (=NH) NH ₂	C1	H	H
850	OH	Ph	H	2- Propionyl amino- succinic acid-1-Y1	H	H	C (=NH) NH ₂	C1	H	H
851	OH	Ph	H	CH ₂ CON(C ₁),	H	H	C (=NH) NH ₂	C1	H	H
852	OH	Ph	H	CH ₂ CONH- (CH ₂) ₃ -OMe	H	H	C (=NH) NH ₂	C1	H	H
853	OH	Ph	H	2-(5- Amino-1- carboxy- pentylcarb- amoyl)- ethylamino	H	H	C (=NH) NH ₂	C1	H	H
854	OH	Ph	H	CH ₂ CONH ₂	H	H	C (=NH) NH ₂	C1	H	H
855	OH	Ph	H	[Bis-(2- methoxy- ethyl)- carbamoyl] -methyl	H	H	C (=NH) NH ₂	C1	H	H
856	OH	Ph	H	2- Hydroxymet- hy1- pyrrolidin -1-Y1-2- oxo-eth-1- Y1	H	H	C (=NH) NH ₂	C1	H	H

EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰
857	OH	Ph	H	CH ₂ CONH- CH ₂ -CF ₃	H	H	C(=NH)NH ₂	C1	H	H
858	OH	Ph	H	Furan-2- ylmethyl- carbamoyl -meth-1- -Y ₁	H	H	C(=NH)NH ₂	C1	H	H
859	OH	Ph	H	Tetrahydro- -furan-2- -ylmethyl)- -carbamoyl -meth-1-Y ₁	H	H	C(=NH)NH ₂	C1	H	H
860	OH	Ph	H	(1,1- Dioxo-1- thiomorph- olin-4- -Y ₁) -2- oxo-eth- -1-Y ₁	H	H	C(=NH)NH ₂	C1	H	H
861	OH	Ph	H	[(Benzoo[1, 3]dioxol- 5- ylmethyl)- -carbamoyl] -meth-1-Y ₁	H	H	C(=NH)NH ₂	C1	H	H
862	OH	Ph	H	[2-(3H- Imidazol- 4-Y ₁) - ethylicarb- amoyl]- meth-1-Y ₁	H	H	C(=NH)NH ₂	C1	H	H
863	OH	Ph	H	(2- Methoxy- 1-methyl- ethylcarb- amoyl)- meth-1-Y ₁	H	H	C(=NH)NH ₂	C1	H	H

EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R'	R ⁸	R ⁹	R ²⁶
864	OH	Ph	H	thiophen-2-ylcarbamoylmethyl	H	H	C(=NH)NH ₂	C1	H	H
865	OH	Ph	H	2-(4-Methyl-piperazin-1-yl)-2-oxoethyl	H	H	C(=NH)NH ₂	C1	H	H
866	OH	Ph	H	I (Pyridin-3-ylmethyl)carbamoyl-methyl	H	H	C(=NH)NH ₂	C1	H	H
867	OH	Ph	H	H	H	H	C(=NH)NH ₂	C1	H	H
868	OH	Ph	H	Br	H	H	C(=NH)NH ₂	C1	H	H
869	OH	Ph	H	O-cyclohexyl	H	H	C(=NH)NH ₂	C1	H	H
870	OH	Ph	H	OMe	H	H	C(=NH)NH ₂	C1	H	H
871	OH	Ph	H	OCH ₂ COOH	H	H	C(=NH)NH ₂	C1	H	H
872	OH	Ph	H	C1	H	H	C(=NH)NH ₂	C1	H	H
873	OH	Ph	H	OCH ₂ CH ₂ NH-acetyl	H	H	C(=NH)NH ₂	C1	H	H
874	OH	Ph	H	OH	H	H	C(=NH)NH ₂	C1	H	H
875	OH	Ph	H	OCH ₂ CH ₂ COOH	H	H	C(=NH)NH ₂	C1	H	H
876	OH	Ph	H	OCH ₂ CH ₂ OH	H	H	C(=NH)NH ₂	C1	H	H
877	OH	Ph	H	H	H	H	C(=NH)NH ₂	F	H	H

EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰
878	OH	Ph	H	OCH ₃ COOH	H	H	C(=NH)NH ₂	F	H	H
879	OH	2- Methyl- cyclohe- xyloxy	H		H	H	C(=NH)NH ₂	F	H	H
879	OH	2- Methyl- cyclohe- xyloxy	H		H	H	C(=NH)NH ₂	F	H	H
879	OH	2- Methyl- cyclohe- xyloxy	H		H	H	C(=NH)NH ₂	F	H	H
879	OH	2- Methyl- cyclohe- xyloxy	H		H	H	C(=NH)NH ₂	F	H	H
879	OH	2- Methyl- cyclohe- xyloxy	H		H	H	C(=NH)NH ₂	F	H	H
879	OH	2- Methyl- cyclohe- xyloxy	H		H	H	C(=NH)NH ₂	F	H	H
880	OH	2- Methyl- cyclohe- xyloxy	H	CH ₃ COOH	H	H	C(=NH)NH ₂	F	H	H
881	OH	2- Methyl- cyclohe- xyloxy	H	CH ₃ CON (Me) ₂	H	H	C(=NH)NH ₂	F	H	H

EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰
882	OH	2- Methyl- cyclohe- xyloxy	H	[bis-(2- methoxy- ethyl)- carbamoyl] -methyl	H	H	C(=NH)NH ₂	F	H	H
883	OH	2- Methyl- cyclohe- xyloxy	H	morpholin- e-4- carbonyl	H	H	C(=NH)NH ₂	F	H	H
884	OH	2- Methyl- cyclohe- xyloxy	H	(2- methoxy- ethylcarb- amoyl)- methyl	H	H	C(=NH)NH ₂	F	H	H
885	OH	2- Methyl- cyclohe- xyloxy	H	CH ₂ -CONH- Me	H	H	C(=NH)NH ₂	F	H	H
886	OH	2- Methyl- cyclohe- xyloxy	H	CH ₂ -CONH- CH ₂ CH ₂ OH	H	H	C(=NH)NH ₂	F	H	H
887	OH	2- Methyl- cyclohe- xyloxy	H	CH ₂ -CON- (CH ₂ CH ₂ OH) ₂	H	H	C(=NH)NH ₂	F	H	H
888	OH	2- Methyl- cyclohe- xyloxy	H	4- hydroxy- piperidin- e-1- carbonyl	H	H	C(=NH)NH ₂	F	H	H
889	OH	2- Methyl- cyclohe- xyloxy	H	thiomorph- oline-4- carbonyl	H	H	C(=NH)NH ₂	F	H	H

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰
890	OH	Ph	H	methanesu lfonylami no- methoxy	H	H	C (=NH) NH ₂	C1	H	H
891	OH	Ph	H	benzoylam ino- methoxy	H	H	C (=NH) NH ₂	C1	H	H
892	OH	Ph	H	I (thiophe ne-2- carbonyl) -amino]- methoxy	H	H	C (=NH) NH ₂	C1	H	H
893	OH	Ph	H	I (morphol ine-4- carbonyl) -amino]- methoxy	H	H	C (=NH) NH ₂	C1	H	H
894	OH	Ph	H	(4- chloro- benzenesu lfonylami no)- methoxy	H	H	C (=NH) NH ₂	C1	H	H
895	OH	Ph	H	OCH ₂ COOH	H	H	C (=NH) NH ₂	C1	H	H
896	OH	Ph	H	OCH ₂ COOEt	H	H	C (=NH) NH ₂	C1	H	H
897	OH	Ph	H	2- methoxy- ethoxycar bonylmeth oxy	H	H	C (=NH) NH ₂	C1	H	H

EX. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ²⁰
898	OH	Ph	H	OCH ₂ CON (Me) ₂	H	H	C(=NH)NH ₂	C1	H	H
899	OH	Ph	H	2-morpholin-4-yl-2-oxo-ethoxy	H	H	C(=NH)NH ₂	C1	H	H
900	OH	Ph	H	2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethoxy	H	H	C(=NH)NH ₂	C1	H	H
901	OH	Ph	H	(1,2-dihydroxy-ethyl)carbamoyl-methoxy	H	H	C(=NH)NH ₂	C1	H	H
902	OH	Ph	H	3-Hydroxy-1-(2-hydroxy-ethyl)-propylcarbamoyl	H	H	C(=NH)NH ₂	C1	H	H

Ex. 801

5 $^1\text{H-NMR}$ ($\text{d}_6\text{-dmsO}$) δ : 3.5 vbn3 9s, 2H), 4.04 (s, 2H), 7.05-
 7.22 (m, 7H), 7.49-7.55 (m, 2H), 8.15 (s, 1H), 8.77 (s,
 2H), 9.21 (s, 2H), 9.42 (s, 1H), 11.75 (s, 1H), 12.33
 (br.s, 1H).

Mass (ESI) M^++1 : Calculated: 477.8, Obs.: 478.3.

Ex. 802

10 $^1\text{H-NMR}$ ($\text{d}_6\text{-dmsO}$) δ : 9.32 (s, 1H), 9.14 (s, 2H), 8.74 (s,
 2H), 8.08 (s, 1H), 7.5 (m, 4H), 7.11 (m, 6H), 4.09 (s, 2H),
 2.69 (t, 2H, $J = 7.4$ Hz), 2.48 (t, 2H, $J = 7.4$ Hz).

Mass (LRMS) M^++1 : Calculated: 491.08; Obs.: 492.7.

15

Ex. 803

10 $^1\text{HNMR}$ (300 MHz, DMSO- d_6) δ : 11.77 (s, 1 H), 9.24 (s, 1 H),
 9.14 (s, 2 H), 8.75 (s , 2 H), 8.05 (s, 1 H), 7.56 - 7.52
 (m, 2 H), 7.44 (s, 1 H), 7.04 - 7.15 (m, 5 H), 4.07 (s, 2
 20 H), 2.2 (s, 3 H).

MS (ESI) Calc for $\text{C}_{23}\text{H}_{21}\text{BrN}_4\text{O}$: 448.11, Found: MH^+ 448.9

Ex. 804

10 $^1\text{H-NMR}$ ($\text{d}_6\text{-dmsO}$) δ : 8.1 (s, 1H), 7.8 (d, 1H, $J = 2.41$ hz),
 7.58 (d, 1H, $J = 10.18$ Hz), 7.52 (d, 1H, $J = 10.2$ Hz), 7.32
 (d, 1H, $J = 2.41$ Hz), 7.2-7.0 (m, 5H), 4.1 (s, 2H).

Mass (ESI) M^++1 : Calculated: 497.01, Obs.: 499.9.

Ex. 805

10 $^1\text{H-NMR}$ ($\text{d}_6\text{-dmsO}$) δ : 11.7 (s, 1H), 9.4 (s, 1H), 9.2 (s, 2H),
 8.7 (s, 2H), 8.06 (br.s, 1H), 7.55 (dd, 1H, $J = 8.57$ Hz),
 7.50 (d, 1H, $J = 8.59$ Hz), 7.28 (d, 1H, $J = 1.52$ Hz), 7.2-
 7.05 (m, 5H), 6.98 (d, 1H, $J = 1.55$ hz), 4.1 (s, 2H), 2.2
 (s, 3H).

35 Mass (ESI) M^++1 : Calculated: 389.88, Obs.: 390.1.

Ex. 807

¹H-NMR (d_6 -dmso)δ : 3.52 (s, 2H), 7.11 (s, 1H), 7.47-7.62 (d, 4H), 8.79 (s, 2H), 9.15 (s, 2H), 9.60 (br.s, 1H), 11.86 (s, 1H).

Mass (ESI) M⁺+1: Calculated: 387.6, Obs.: 388.2.

Ex. 808

¹H-NMR (d_6 -dmso)δ : 8.05 (s, 1H), 7.6-6.9 (m, 10H), 4.1 (s, 2H).

Mass (ESI) M⁺+1: Calculated: 375.11, Obs.: 375.9.

Ex. 809

¹H-NMR (d_6 -dmso)δ : 3.38 (s, 2H), 6.96 (s, 1H), 7.45-7.64 (m, 4H), 8.18 (s, 1H), 8.83 (s, 2H), 4.20 (s, 2H), 9.58 (br.s), 11.91 (s, 1H).

Mass (ESI) M⁺+1: Calculated: 387.2, Obs.: 386.9.

Ex. 810 2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine

¹H NMR (DMSO- d_6) δ : 9.16 (s, 2H), 8.70 (s, 2H), 8.14 (s, 1H), 7.61 (d, 1H, J = 8.66 Hz), 7.58 (d, 1H, J = 1.49 Hz), 7.54 (dd, 1H, J = 8.66 Hz), 7.41 (d, 1H, J = 1.24 Hz), 7.14 (s, 1H), 2.30 (s, 3H).

MS: 343.03 (calc); 344 (obs.)

Ex. 811

¹H-NMR (d_6 -dmso)δ: 11.8 (s, 1H), 9.7 (s, 1H), 9.2 (s, 2H), 8.8 (s, 2H), 8.12 (s, 1H), 7.6 (d, 1H, J=8.62 Hz), 7.57 (br.s, 1H), 7.52 (d, 1H, J=8.73 Hz), 7.24 (br.s, 1H), 7.16 (s, 1H), 2.3 (s, 3H).

Mass. (M⁺+1): Calculated: 299.08; Observed: 279.8.

EX. 812 2-(3,5-Dichloro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine

5 ^1H NMR (CD₃OD) δ: 8.14 (d, 1H, J = 1.7 Hz), 7.74 (d, 1H, J = 2.7 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.57 (dd, 1H, J = 1.7, 8.1 Hz), 7.4 (d, 1H, J = 2.7 Hz), 7.25 (s, 1H).
 MS: 319.0 (calc.); 319.7 (obs.).

Ex. 813

10 $^1\text{H-NMR}$ (d₆-dmsO)δ : 12.1 (s, 1H), 10.21 (s, 1H), 9.2 (s, 2H), 8.8 (s, 2H), 8.32 (s, 1H), 8.2 (s, 1H), 8.1 (d, 1H, J = 1.98 Hz) 8.05 (s, 1H), 7.6 (d, 1H, J = 8.56 Hz), 7.55 (dd, 1H, J = 8.67 Hz), 7.46 (s, 1H), 7.2 (s, 1H).
 Mass (ESI) M⁺+1: Calculated: 372.04, Obs.: 372.8.

15

Ex. 814

10 $^1\text{H-NMR}$ (d₆-dmsO)δ : 11.7 (s, 1H), 9.1 (s, 2H), 8.69 (s, 2H), 8.49 (s, 1H), 8.0 (s, 1H), 7.6-7.4 (m, 2H), 7.2-7.0 (m, 5H), 6.99 (d, 1H, J = 0.5 Hz), 6.86 (d, 1H, J = 1.32 Hz), 4.1 (s, 2H), 2.25 (s, 3H), 2.15 (s, 3H).
 Mass (ESI) M⁺+1: Calculated: 369.46, Obs.: 370.1.

EX. 815 2-(3,5-Difluoro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine

25

MS: 287.1 (calc.); 287.8 (obs.).

Ex. 816

10 $^1\text{H-NMR}$ (d₆-dmsO)δ : 11.7 (s, 1H), 9.75 (s, 1H), 9.15 (s, 2H), 8.69 (s, 2H), 8.19 (s, 1H), 7.82 (s, 1H), 7.57 (d, 1H, J = 8.57 Hz), 7.55-7.4 (m, 2H), 2.25 (s, 2H).
 Mass (ESI) M⁺+1: Calculated: 420.98, Obs.: 424.6.

35

Ex. 817 2-(2-Hydroxy-5-methyl-3-thiophen-2-yl-phenyl)-1H-indole-5-carboxamidine

5 ^1H NMR (DMSO-d₆): δ 9.12 (s, 2H), 8.70 (s, 2H), 8.11 (d, 1H, J = 1.68 Hz), 7.70-7.77 (m, 1H), 7.63-7.46 (m, 5H), 7.24 (d, 2H, J = Hz), 7.09 (s, 1H), 2.32 (s, 3H).
 MS: 347.11 (calc); 348.0 (obs.).

Ex. 818

10 $^1\text{H-NMR}$ (d₆-dmso) δ : 11.8 (s, 1H), 9.9 (s, 1H), 9.2 (s, 2H), 8.7 (s, 2H), 8.2 (s, 1H), 8.0-7.4 (m, 3H), 7.2 (s, 1H), 3.5 (s, 2H), 2.2 (s, 3H).
 Mass (ESI) M⁺+1: Calculated: 369.18, Obs.: 400.9.

15

Ex. 819

15 $^1\text{H-NMR}$ (d₆-dmso) δ : 12.0 (s, 1H), 10.0 (s, 1H), 8.8 (s, 2H), 8.15 (s, 1H), 7.95 (d, 1H, 2.38 Hz), 7.76 (d, 1H, J = 2.33 Hz), 7.60 (d, 1H, J = 8.44 Hz), 7.55 (d, 1H, J = 8.47 hz), 7.24 (s, 1H).
 20 Mass (ESI) M⁺+1: Calculated: 406.97, Obs.: 409.8.

Ex. 821 2-(2-hydroxybiphen-3-yl)-5-amidinoindole hydrochloride

25 $^1\text{H NMR}$ (DMSO-d₆) δ : 11.6 (s, 1H), 9.16 (s, 2H), 8.96 (s, 1H), 8.15 (s, 1H), 7.74 (dd, 1H, J = 7.67 Hz), 7.64 (d, 1H, J = 8.66 hz), 7.57-7.35 (m, 5H), 7.25 (dd, 1H, J = 7.67 Hz), 7.12 (s, 1H), 7.11 (t, 1H, J = 7.67 Hz).
 MS: 327.14 (calc.); 327.7 (obs.).

30

Ex. 822

15 $^1\text{H-NMR}$ (d₆-dmso) δ : 11.7 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 8.65 (s, 2H), 8.05 (s, 1H), 7.53 (m, 1H), 7.3-7.0 (m, 9H), 4.1 (s, 2H).
 35 Mass (ESI) M⁺+1: Calculated: 375.11, Obs.: 376.0.

Ex. 823

¹H-NMR (d_6 -dmsO) δ : 7.28 (s, 1H), 7.57 (d, 1H, J = 8.4 Hz),
 7.62 (d, 1H, J = 8.4 Hz), 8.19 (s, 1H), 8.39 (d, 1H, J =
 1.2 Hz), 8.61 (d, 1H, J = 1 Hz), 8.84 (s, 2H), 9.21 (s,
 5 2H), 12.3 (s, 1H).

Mass (ESI) M⁺+1: Calculated: 375.2, Obs.: 375.6.

Ex. 825

¹H-NMR (d_6 -dmsO) δ : 11.8 (s, 1H), 9.15 (s, 2H), 8.8 (s, 2H),
 10 8.1 (s, 1H), 7.85 (d, 1H, J = 1.64 Hz), 7.62 (d, 1H, J =
 8.51 Hz), 7.52 (d, 1H, J = 8.45 Hz), 7.25 (s, 1H), 7.3-7.2
 (m, 1H), 7.05 (d, 1H, J = 8.73 Hz).

Mass (ESI) M⁺+1: Calculated: 265.12, Obs.: 285.8

15

Ex. 826

¹H-NMR (d_6 -dmsO) δ : 11.8 (s, 1H), 9.2 (s, 2H), 8.7 (s, 2H),
 8.2 (s, 1H), 8.0-7.4 (m, 3H), 7.2 (s, 1H), 3.6 (s, 2H), 2.2
 (s, 3H).

Mass (ESI) M⁺+1: Calculated: 401.06, Obs.: 401.9.

20

Ex. 827

¹H-NMR (d_6 -dmsO) δ : 11.8 (s, 1H), 9.16 (s, 2H), 8.85 (s, 2H),
 8.1 (s, 1H), 7.6 (d, 8.58, J =8.58 Hz), 7.5 (d, 1H, J = 8.64
 Hz), 7.4 (s, 1H), 7.1 (s, 1H), 6.9 (s, 1H), 2.24 (s, 3H).

25 Mass.: Calc. 279.14; Obs.: 279.8.

Ex. 828 2-(2-Hydroxy-5,4'-dimethyl-biphenyl-3-yl)-1H-indole-5-carboxamidine

¹H NMR (DMSO- d_6) δ : 9.15 (s, 2H), 8.75 (s, 2H), 8.65 (s,
 30 1H), 8.21 (s, 1H), 8.13 (s, 1H), 7.63 (d, 1H, J = 8.66 Hz),
 7.54-7.51 (m, 2H), 7.43 (d, 2H, 2H), 7.27 (d, 2H, J = 7.67
 Hz), 7.11 (s, 1H), 7.04 (d, 1H, J = 1.73 Hz), 2.36 (s, 3H),
 2.33 (s, 3H).

MS: 355.17 (calc.); 356.1 (obs.).

35

Ex. 829

¹H NMR (D₆-DMSO) δ: 7.03 (d, 1H, J = 8.75), 7.25 (s, 1H), 7.34 (dd, 1H, J = 8.75, 2.3), 7.54 (dd, 1H, J = 8.59), 7.63 (d, 1H, J = 8.59), 7.98 (d, 1H, J = 2.3), 8.13 (s, 1H), 8.86 (s, 2H), 9.18 (s, 2H), 10.76 (s, 1H), 11.84 (s, 1H).

Mass Bioion (M+H⁺): Calculated: 329.02; Obs.: 330.5.

Ex. 830

¹H-NMR (d₆-dmso)δ : 11.7 (s, 1H), 10.1 (s, 1H), 9.15 (s, 2H), 8.7 (s, 2H), 8.1 (s, 1H), 7.62 (d, 1H, J = 8.65 Hz), 7.60 (s, 1H), 7.5 (d, 1H, J = 8.64 Hz), 7.1 (s, 1H), 7.0 (d, 1H, J = 8.46 Hz), 6.9 (d, 1H, 8.0 hz), 2.25 (s, 3H).

Mass (ESI) M⁺+1: Calculated: 265.12; Obs.: 265.9.

15

Ex. 836

¹H-NMR (300 MHz, DMSO-d₆) δ: 11.99 (s, 1H), 9.18 (s, 2H), 8.80 (s, 2H), 8.12 (s, 1H), 7.77 (d, 1H, J = 7.5 Hz), 7.63 (m, 2H), 7.53 (m, 3H), 6.67 (s, 1H). MS (+ESI); m/z 280.1 (MH⁺). calcd. for C₁₆H₁₄N₃O₂; m/z 280.1.

Ex. 837

¹H-NMR (d₆-dmso)δ : 11.8 (s, 1H), 9.25 (s, 1H), 9.15 (s, 2H), 8.7 (s, 2H), 8.08 (s, 1H), 7.57 (d, 1H, J = 8.46 Hz), 7.51 (d, 1H, J = 8.57 Hz), 7.44 (d, 1H, J = 1.25 Hz), 7.25 -7.05 (m, 5), 7.0 (d, 1H, J = 1.51 Hz), 4.1 (s, 2H), 2.22 (s, 3H).

Mass (ESI) M⁺+1: Calculated: 433.10, Obs.: 434.0.

30 **Ex. 841 3-(4-nitro-benzyl)-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine**

¹HNMR (300 MHz, DMSO) δ: 11.84 (s, 1 H), 9.24 (s, 1 H), 9.11 (s, 2 H), 8.70 (s, 2 H), 8.06 (d, 2 H, J = 7.6 Hz), 8.04 (s, 1 H), 7.60-7.56 (m, 2 H), 7.36 (s, 1 H), 7.34 (d, 2 H, J = 7.6 Hz), 6.03 (s, 1 H), 4.21 (s, 2 H), 2.20 (s, 3 H).

MS (ESI) Calc for C₂₃H₁₉BrN₄O₃: 478.08, Found: MH+ 479.4.

Ex. 843

Mass (ESI) M⁺+1: Calculated: 309.1; Obs.: 309.7.

5

UTILITY

Compounds of the present invention are useful as inhibitors of proteases, which play a significant role in 10 the progression of cancer. Their inhibitory activity includes inhibition of urokinase (uPA) which has been postulated to have therapeutic value in treating cancer.

The compounds of this invention are also useful as anticoagulants for the treatment or prevention of 15 thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example unstable angina, first or recurrent ischemic attack, stroke, atherosclerosis, 20 venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to the inhibition of Factor Xa (FXa), Factor VIIa (FVIIa), and thrombin.

Some of the compounds of the present invention show 25 selectivity between uPA and FXa, with respect to their inhibitory properties. The effectiveness of compounds of the present invention as inhibitors of Urokinase and Factor Xa is determined using synthetic substrates and 30 purified Urokinase and purified human Factor Xa respectively.

The rates of hydrolysis by the chromogenic substrates were measured both in the absence and presence of compounds 35 of the present invention. Hydrolysis of the substrates result in the release of the -pNA moiety, which is monitored spectrophotometrically by measuring the increase in absorbance at 405 nano meter (nm). A decrease in the rate of absorbance change at 405 nm in the presence of a

inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as the inhibitory constant, K_i app.

Factor Xa determinations were made in 50 mM Tris buffer, pH 7.5, containing 1M NaCl, 5 mM CaCl₂, 0.05% Tween-20, and 1.5 mM EDTA. Values of K_i app. were determined by allowing 2-3 nM human Factor Xa (Haematologic Technologies, VT, USA) to react with the substrate (1 mM) in the presence of an inhibitor. Hydrolysis of the chromogenic substrate is followed spectrophotometrically at 405 nm for five minutes. The enzyme assay routinely yielded linear progression curves under these conditions. Initial velocity measurements calculated from the progress curves by a kinetic analysis program (Batch K_i ; Peter Kuzmic, BioKin, Ltd., Madison, WI) were used to determine K_i app.

Urokinase inhibition determinations were made in 50 mM Tris (pH7.5), 150 mM NaCl, 0.05% Tween-20, 0.002% antifoam, and 1 mM EDTA. human Urokinase (from American Diagnostica, CT, USA). Values of K_i app. were determined by allowing 20 nM human Urokinase to react with the Pefachrome substrate (0.3 mM, Centerchem, CT, USA) in the presence of an inhibitor. Hydrolysis of the chromogenic substrate is followed spectrophotometrically at 405 nm for five minutes. The enzyme assay routinely yielded linear progression curves under these conditions. Initial velocity measurements calculated from the progress curves by a kinetic analysis program (Batch K_i ; Peter Kuzmic, BioKin, Ltd., Madison, WI) were used to determine K_i app.

Table IV lists inhibition constants (K_i app.) for representative compounds of the present invention. These values are for uPA and FXa.

Table IV

Ex.	uPA	FXa
	Ki μ M	Ki μ M
110	0.51	
116	0.651	
258		0.46
291	0.85	0.85
802	0.26	0.000618
820	0.065	0.298
877	2.5	0.033
860	0.004	5.4

5

Definitions

The compounds of the present invention may have
 10 asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. Many geometric isomers of olefins, C=N double bonds, and the like can be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of
 15 isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure (representing a compound of Formula I) are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

20 As used herein, the following terms and abbreviations have the following meaning, unless indicated otherwise.

The term "prodrug" is intended to represent covalently bonded carriers which are capable of releasing the active ingredient of Formula I, when the prodrug is administered to a mammalian subject. Release of the active ingredient occurs in vivo. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups however regenerate original functional groups by routine manipulation or in vivo. Prodrugs of compounds of Formula I include compounds wherein a hydroxy, amidino, guanidino, amino, carboxylic or a similar group is modified.

"Pharmaceutically acceptable salts" is as understood by one skilled in the art. Thus a pharmaceutically acceptable salt includes acid or base salts of compounds of Formula I. Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "optionally is substituted with one to three substituents" means that the group referred to may or may not be substituted in order to fall within the scope of the invention. Thus the term "optionally substituted" is intended to mean that any one or more hydrogens on a designated atom can be replaced with a selection from the

indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound. When the substituent is keto (=O) then 2 hydrogens on the atom are replaced. "Optional
5 substituents", unless otherwise indicated, are independently selected from a group consisting of H; N(R¹⁰)₂; NO₂; halogen; aryl; O-C₅₋₁₀ cyclo alkyl substituted with R¹⁰; guanidino; urea; thio urea; amidino; para or meta phenoxy; piperidin-4-yloxy; 4-amino-cyclohexyloxy; 1-(1-
10 Imino-ethyl)-piperidin-4-yloxy; 1-(1-Imino-ethyl)-pyrrolidin-3-yloxy; 2-Amino-3-methyl-butyryl; 4-Acetimidoylamino-cyclohexyloxy; 1-(1-Imino-ethyl)-pyrrolidin-2-ylmethoxy; 2-(2-Hydroxycarbonimidoyl-pyridin-3-yloxy)-ethoxy; 3,4-Dicyano-phenoxy; SC₁₋₄ alkyl, S-
15 aryl, O-C₁₋₄ alkyl, COOR¹⁰, C(O)-pyrrolidine; C(O)CH(NH₂)CH₂OH; C(O)CH(NH₂)CH₂Ph; C(O)CH(NH₂)CH₂COOH; O-pyrrolidine; C(O)-(CH₂)₁₋₃-imidazole; SO₂-N(alkyl)₂; C(=N)-C₃; O-piperidine; 2-aminothiazol-5-ylmethoxy; O-CH₂-COOH; pyrrolidine-2-ylmethoxy; 2,4,6-triamino pyrimidin-5-
20 ylmethoxy; NH-SO₂-alkyl; NHC₁-C₄ alkyl; N(C₁-C₄)₂ alkyl; CF₃; C₂₋₁₀ alkenyl and C₁₋₁₀ alkyl.

The term "alkyl", as used herein, is intended to include branched and straight chain saturated aliphatic hydrocarbon groups having from 1 to 14 or the specified number of carbon atoms, illustrative examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, and n-hexyl. "Alkenyl" is intended to include a branched or straight chain hydrocarbon group having one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. The term "alkelene" represents an alkyl group, as defined above, except that it has at least one center of unsaturation, i.e., a double bond. Illustrative examples are butene, propene, and pentene. The term "cycloalkyl", "cycloalkyl ring", "cycloalkyl radical" or "cyclic hydrocarbon" indicates a saturated or partially

unsaturated three to fourteen carbon monocyclic or bicyclic hydrocarbon moiety which is optionally substituted with an alkyl group. Illustrative examples include cyclo propyl, cyclo hexyl, cyclo pentyl, and cyclo butyl. The term 5 "alkoxy" as used herein represents -OC₁₋₆ alkyl.

The terms "Ar" and "aryl", as used herein, are intended to represent a stable substituted or unsubstituted (collectively also referred to as 'optionally substituted') six to fourteen membered mono-, bi- or tri-cyclic 10 hydrocarbon radical comprising carbon and hydrogen atoms. Illustrative examples are phenyl (Ph), naphthyl, anthracyl groups, and piperanyl. It is also intended that the terms "carbocycle" and "carbocyclic" include "Ar", "aryl" as well as "cyclo alkyl" groups, which are defined above. 15 "Halogen" or "halo", as used herein, represents Cl, Br, F or I.

As used herein the term "bicyclic heterocyclic ring structure" is intended to represent a stable 7 to 10 membered bicyclic heterocyclic ring which is partially 20 unsaturated or unsaturated (aromatic, i.e., heteroaryl) and which consists of carbon atoms and from 1 to 3 hetero atoms selected from S, O, and N, preferably nitrogen atoms. The nitrogen and sulfur atoms can exist in their respective oxidized states, while the nitrogen atom can also exist in 25 its quaternized form. Illustrative examples of the bicyclic heterocyclic ring structure are 3H-imidazo[4,5-c]pyridine-2-yl, 1H-imidazo[4,5-c]pyridine-2-yl, 3H-pyrrolo[3,2-c]pyridine-2-yl, 3H-pyrrolo[3,2-c]pyrimidine-2-yl, thiazolo[5,4-c]pyridine-2-yl, oxazolo[5,4-c]pyridine-2-yl, 30 4H-thiopyrano[4,3-d]oxazole, 1H-indole-2-yl, 1H-benzimidazole-2-yl, 2,3-dihydro, 1H-indole-2-yl, 2,5-dihydro-thiopyrano[2,3-b]pyrrole, thieno[2,3-c]pyridine, 4,5-dihydro-1H-benzoimidazole-2-yl, 1H-pyrrolo[2,3c]pyridine, benzooxazole, 4H-thiopyrano[4,3-35 b]furan, 4,5-dihydrofuro[3,2-b]pyridine, 1,7-dihydro-thiopyrano-[2,3-b]pyrrole-2-yl, 1,4-dihydro-thiopyrano-[3,4-d]imidazole-2-yl, and 1,5-dihydro pyrano[2,3-

d]imidazole-2-yl. It is preferred that when the total number of hetero atoms in the heterocycle exceeds 1, then the heteroatoms are not adjacent to one another. Preferred bicyclic heterocyclic ring structures comprise 9 to 10 5 membered bicyclic heterocyclic ring structures comprising a six membered ring and a five membered ring fused together such that the two rings have two common atoms. Illustrative examples of the preferred bicyclic heterocyclic ring structures are 1H-indole-2-yl, 1H-10 benzimidazole-2-yl.

The term "heteroaryl" is intended to represent a stable 5 to 10 membered aryl group ("aryl" as defined above), wherein one or more of the carbon atoms is replaced by a hetero atom selected from N, O, and S. The 15 hetero atoms can exist in their chemically allowed oxidation states. Thus a Sulfur (S) atom can exist as a sulfide, sulfoxide, or sulfone. Preferred heteroaryl groups are six membered ring systems comprising not more than 2 hetero atoms. Illustrative examples of preferred 20 heteroaryl groups are thienyl, N-substituted succinimide, 3-(alkyl amino)-5,5-dialkyl-2-cyclohexen-1-one, methyl pyridyl, alkyl theophylline, furyl, pyrrolyl, indolyl, pyrimidinyl, isoxazolyl, purinyl, imidazolyl, pyridyl, pyrazolyl, quinolyl, and pyrazinyl. The term 25 "heterocycloalkyl" means a stable cyclo alkyl group containing from 5 to 14 carbon atoms wherein one or more of the carbon atoms is replaced by a hetero atom chosen from N, O and S. The hetero atoms can exist in their chemically allowed oxidation states. Thus Sulfur (S) can exist as a 30 sulfide, sulfoxide, or sulfone. The heterocycloalkyl group can be completely saturated or partially unsaturated. Illustrative examples are piperidine, 1,4-dioxane, and morpholine.

As used herein the terms "heterocyclyl", 35 "heterocyclic" and/or "het" are intended to represent a stable 5- to 7- membered monocyclic or 7- to 10- membered bicyclic heterocyclic ring which is saturated, partially

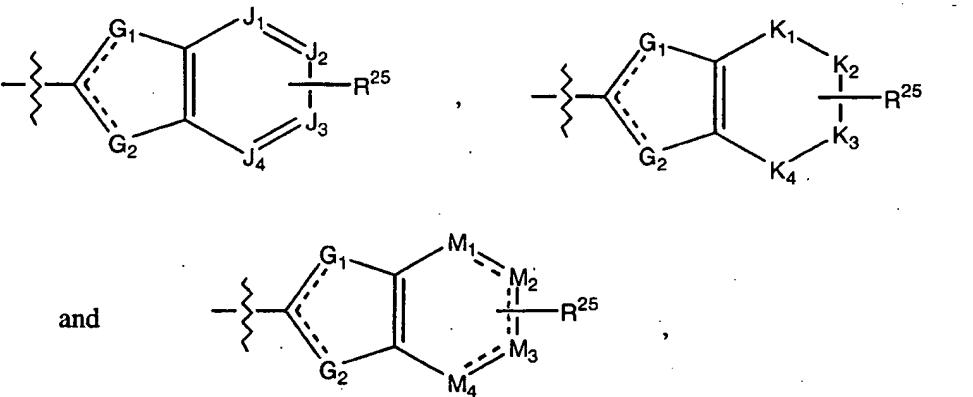
unsaturated, or unsaturated (aromatic), which consists of carbon atoms and from one to 4 hetero atoms independently selected from a group consisting of N, O and S. The nitrogen and the sulfur hetero atoms can exist in their respective oxidized states. The heterocyclic ring may be attached to its pendent group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on a carbon or a nitrogen atom if the resulting compound is stable. The nitrogen in the heterocycle can exist in its quaternized form. It is preferred that when the total number of hetero atoms in the heterocycle exceeds 1, then the heteroatoms are not adjacent to one another. It is understood that the terms "heterocyclyl", "heterocyclic", and "het" include the terms "heteroaryl", "heterocycloalkyl" and "bicyclic heterocyclic ring structure" as described above.

Preferred "heterocyclyl", "heterocyclic" and/or "het" groups are selected from 1-(2-Hydroxymethyl-pyrrolidin-1-yl)-2,3-dimethyl-butan-1-one, 3-Pyridin-2-yl-propan-1-ol, N-(2,3-Dimethoxy-benzyl)-2-hydroxy-acetamide, 1-Methyl-2-m-tolyl-1H-benzoimidazole-5-carboxamidine, 2-Methyl-3,4,6,7-tetrahydro-imidazo[4,5-c]pyridine-5-carboxamidine, 2-Amino-3-hydroxy-1-(2-methyl-3,4,6,7-tetrahydro-imidazo[4,5-c]pyridin-5-yl)-propan-1-one, 2-Amino-1-(2-methyl-3,4,6,7-tetrahydro-imidazo[4,5-c]pyridin-5-yl)-ethanone, 2-Methyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine, N-o-Tolyl-methanesulfonamide, 2-Methyl-benzothiazole, 3-Amino-1-(2-hydroxymethyl-pyrrolidin-1-yl)-propan-1-one, 2-Hydroxy-1-(2-hydroxymethyl-pyrrolidin-1-yl)-ethanone, 2-(2-Hydroxy-ethyl)-indan-1,3-dione, 5-Fluoro-2-methyl-1H-benzoimidazole, 2-Methyl-1H-imidazo[4,5-c]pyridine, 2-Hydroxy-N-(2-morpholin-4-yl-ethyl)-acetamide, 2-Methyl-1H-imidazo[4,5-b]pyridine, 2-Amino-1-(3-methyl-piperidin-1-yl)-ethanone, 2-Methyl-1H-benzoimidazol-4-ol, 2-Pyridin-2-yl-ethanol, N-(3-Hydroxy-propyl)-2-phenyl-acetamide, N-(3-Hydroxy-propyl)-3-phenyl-propionamide, N-(3-Hydroxy-propyl)-benzamide, N-(2-Hydroxy-

ethyl)-2-phenyl-acetamide, (4-Hydroxy-butyl)-carbamic acid tert-butyl ester, (2-Hydroxy-ethyl)-carbamic acid benzyl ester, (4-Hydroxy-piperidin-1-yl)-phenyl-methanone, 4-Bromo-2-methoxy-benzylamine, 3-Methoxy-5-trifluoromethyl-benzylamine, N-(3,5-Dimethoxy-benzyl)-acetamide, 2-Methyl-1H-benzoimidazole-5-carboxamidine, and 2-Hydroxy-N-naphthalen-1-yl-acetamide.

The following structural representations further illustrate the term "het":

10



wherein G_1 and G_2 independently at each occurrence represent $S(O)_{0-2}$, NH , $N-R^{24}$, O , CR^{10} , or CHR^{10} ; J_1 , J_2 , J_3 , and J_4 independently represent CR^{10} or N , wherein at least two of J_1 , J_2 , J_3 , and J_4 represent CH ; K_1 , K_2 , K_3 and K_4 independently represent $-NHR^{10}$, $-NHR^{24}$, $-CHR^{10}$, $-CH-C(=NH)-NH_2$, or $N-C(=NH)-NH_2$ wherein at least two of K_1 , K_2 , K_3 and K_4 represent CH_2 ; M_1 , M_2 , M_3 and M_4 independently represent $-NHR^{10}$, $-NHR^{24}$, $-CHR^{10}$, $-CH-C(=NH)-NH_2$, or $N-C(=NH)-NH_2$, wherein at least two of M_1 , M_2 , M_3 and M_4 represent CH or CH_2 ; and R^{25} represents H , halogen, $-C_{1-6}$ alkyl, $-NO_2$, NHR^{10} , $NH-SO_2-R^{10}$, $-OH$, C_{1-6} alkoxy, amidino, guanidino, $-COOR^{10}$, or $-CONHR^{10}$. The variables R^{10} and R^{24} are as defined earlier. The dashed lines indicate optional unsaturation without violating the valency rules.

The term "basic group" as used under R^7 and R^8 , defined earlier, is intended to represent amidino, guanidino, $-C(=NH)N(R^{10})_2$, 2-imidazoline, $-N$ -amidinomorpholine, N -

5 substituent, which can represent Q, Q¹, Q², Q³, L¹, L², L³ and L⁴, is a group wherein the nitrogen atom (N) is the annular ring atom substituted with a natural or unnatural amino acid side chain (natural or unnatural amino acid side chain is a defined above). The point of attachment between the nitrogen atom and the natural or unnatural amino acid side chain is at the keto (C=O) group of the respective amino acids. Thus a N-natural amino acid, i.e., N-cysteine, is N-C(=O)-CH(NH₂)-CH₂-SH.

10

CLAIMS

1. A compound of Formula I:

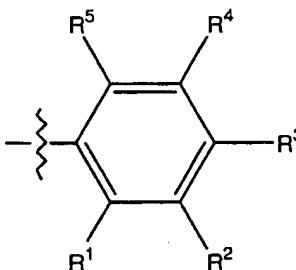
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A-B

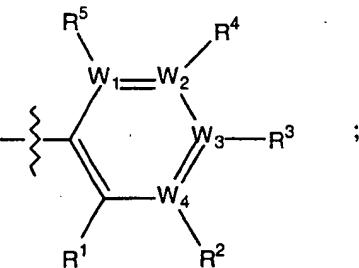
its prodrug forms, or pharmaceutically acceptable salts thereof, wherein

10 A represents a saturated, unsaturated, or a partially unsaturated bicyclic heterocyclic ring structure substituted with R⁶, R⁷, R⁸, R⁹, and R²⁰;
 B represents

15



or



15

R¹ represents OH, halogen, COOH, COO-C₁₋₄ alkyl, O-(CH₂)₀₋₁-Ph, N(R¹⁰)₂, CH₂OR¹⁰, C₁₋₆ halogenated alkyl, O-(CH₂)₁₋₄-CO-N(R¹⁰)₂, SC₁₋₄ alkyl, NHSO₂C₁₋₄ alkyl, SO₂-OH, O-SO₂-OH, O-SO₂-O-C₁₋₄

20 alkyl, OP(O)(OH)₂, or OPO₃C₁₋₄ alkyl;

R², R³, R⁴, and R⁵ independently at each occurrence represent H, SH, OR¹⁰, halogen, COOR¹⁰, CONR¹¹R¹², optionally substituted aryl, optionally substituted heterocyclyl, C₄₋₁₄ cycloalkyl-C₁₋₄ alkyl, C₁₋₄ alkyl aryl, optionally substituted C₁₋₁₄

25 straight chain, branched or cyclo alkyl, O-(CH₂)₂₋₆-NR¹⁰-(CH₂)₀₋₃-R²⁴, NR¹⁰R²⁴, (CH₂)₁₋₄-NR³³R³⁴, (CH₂)₁₋₄-COOR³³, O-(CH₂)₁₋₃-CO-het, O-(CH₂)₁₋₂-NH-CO-aryl, O-(CH₂)₁₋₂-NR¹⁰-CO-NR¹⁰R³³, O-(CH₂)₀₋₂-C(O)-NR³³R³⁴, O-(CH₂)₁₋₄-COOR¹⁰, O-(CH₂)₁₋₃-het-R³², O-optionally

substituted cycloalkyl, O-(CH₂)₁₋₄-NR¹⁰-COO-t-butyl, O-(CH₂)₁₋₄-NR¹⁰R³³, O-(CH₂)₁₋₄-NR¹⁰-C(O)-C₀₋₃-alkyl-optionally substituted aryl,

30 O-substituted cycloalkyl, O-(CH₂)₀₋₆-optionally substituted aryl, (CH₂)₁₋₄-NH-C(O)O-(CH₂)₁₋₄-PhR¹³R¹⁴, NO₂, O-

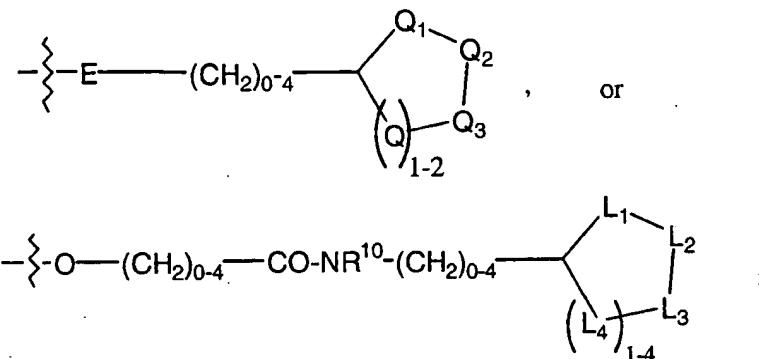
amidino piperidine, 4-hydroxy-N-amidino piperidine, N-amidino pyrrolidine, tetrahydro pyrimidine, and thiazolidin-3-yl-methylideneamine. The compounds of the present invention were named using the "Autonom", a Beilstein Commander 2.1 Application, distributed by Beilstein.

The term "natural amino acid", as used herein is intended to represent the twenty naturally occurring amino acids in their 'L' form, which are some times also referred as 'common amino acids', a list of which can be found in *Biochemistry*, Harper & Row Publishers, Inc. (1983). The term "unnatural amino acid", as used herein, is intended to represent the 'D' form of the twenty naturally occurring amino acids described above. It is further understood that the term unnatural amino acid includes homologues of the natural amino acids, and synthetically modified form of the natural amino acids. The synthetically modified forms include amino acids having alkylene chains shortened or lengthened by up to two carbon atoms, amino acids comprising optionally substituted aryl groups, and amino acids comprised halogenated groups, preferably halogenated alkyl and aryl groups.

The term "natural amino acid side chain" is intended to represent a natural amino acid ("natural amino acid" as defined above) wherein a keto (C=O) group replaces the carboxylic acid group in the amino acid. Thus, for example, an alanine side chain is C(=O)-CH(NH₂)-CH₃; a valine side chain is C(=O)-CH(NH₂)-CH(CH₃)₂; and a cysteine side chain is C(=O)-CH(NH₂)-CH₂-SH. The term "unnatural amino acid side chain" is intended to represent an unnatural amino acid ("unnatural amino acid" as defined above) wherein a keto (C=O) group replaces the carboxylic acid group forming unnatural amino acid side chains similar to ones illustrated under the definition of "natural amino acid side chain" above.

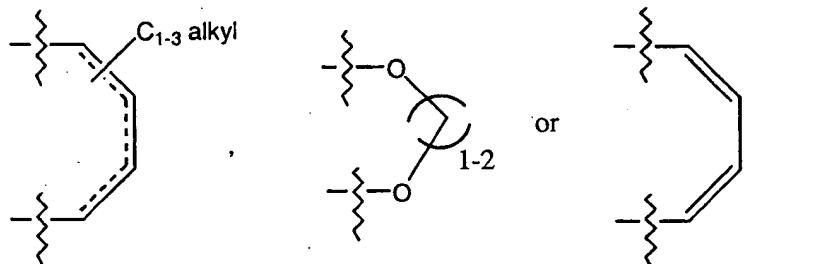
It thus follows that a "N-natural amino acid side chain" substituent and "N-unnatural amino acid side chain"

$(\text{CH}_2)_{0-4}-\text{C}(\text{O})-\text{NH}$ -tetrahydro carboline, $\text{NR}^{10}\text{R}^{28}$, $\text{O}-(\text{CH}_2)_{1-3}-$ optionally substituted het, $\text{CH}_2\text{COOCH}_3$, $\text{CH}=\text{CH-COOCH}_3$, 5-amidino benzimidazole,



5

alternatively R^2 and R^3 taken together form



10 R^6 and R^9 independently at each occurrence represents H, halogen, cyano, C_{1-4} alkyl, C_{1-4} halogenated alkyl, NO_2 , O-aryl or OR^{11} ;

15 R' and R^8 independently at each occurrence represent OH, CF_3 , H, NO_2 , C_{1-4} alkyl, OC_{1-4} alkyl, or O-aryl, halogen, cyano, or a basic group selected from guanidino, $\text{C}(=\text{NH})\text{N}(\text{R}^{10})_2$, $\text{C}(=\text{NH})-\text{NH}-\text{NH}_2$, $\text{C}(=\text{O})\text{NH}_2$, 2-imidazoline, N-amidinomorpholine, N-amidino piperidine, 4-hydroxy-N-amidino piperidine, N-amidino pyrrolidine, tetrahydro pyrimidine, and thiazolidin-3-yl-methylideneamine; with the proviso that only one of R' and R^8 represent a basic group;

20 R^{10} independently at each occurrence represents H, $(\text{CH}_2)_{0-2}$ -aryl, C_{1-4} halo alkyl, or C_{1-14} straight chain, branched or cyclo alkyl, and alternatively, when one atom is substituted with two R^{10} groups, the atom along with the R^{10} groups can form a five to 10 membered ring structure;

R¹¹ and R¹² independently at each occurrence represent H or C₁₋₄ alkyl;

R²⁰ represents R²⁴, C₁₋₄-alkyl, (CH₂)₁₋₃-biphenyl, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl)₂, (CH₂)₁₋₄-NH-C(O)-R²⁴, (CH₂)₁₋₄-NH-SO₂-R²⁴,

5 halogen, COOR¹⁰, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl), (CH₂)₁₋₄-NR¹⁰-C(O)-R²⁴, (CH₂)₁₋₄-NR¹⁰-SO₂-R²⁴, (CH₂)₁₋₄-het, (CH₂)₁₋₄-CON(R¹⁰)₂, (CH₂)₁₋₄-N(R¹⁰)-C(O)-NR¹⁰R²⁴, (CH₂)₁₋₄-N(R¹⁰)-C(S)-NR¹⁰R²⁴, or (CH₂)₁₋₃-COOH;

10 R²⁴ represents R¹⁰, (CH₂)₁₋₄-optionally substituted aryl, (CH₂)₀₋₄OR¹⁰, CO-(CH₂)₁₋₂-N(R¹⁰)₂, CO(CH₂)₁₋₄-OR¹⁰, (CH₂)₁₋₄-COOR¹⁰, (CH₂)₀₋₄-N(R¹⁰)₂, SO₂R¹⁰, COR¹⁰, CON(R¹⁰)₂, (CH₂)₀₋₄-aryl-COOR¹⁰, (CH₂)₀₋₄-aryl-N(R¹⁰)₂, or (CH₂)₁₋₄-het-aryl;

15 R²⁸ represents (CH₂)₁₋₂-Ph-O-(CH₂)₀₋₂-het-R³⁰, C(O)-het, CH₂-Ph-CH₂-het-(R³⁰)₁₋₃; (CH₂)₁₋₄-cyclohexyl-R³¹, CH₂-Ph-O-Ph-(R³⁰)₁₋₂, CH₂-(CH₂OH)-het-R³⁰, CH₂-Ph-O-cycloalkyl-R³¹, CH₂-het-C(O)-CH₂-het-R³⁰, or CH₂-Ph-O-(CH₂)-O-het-R³⁰;

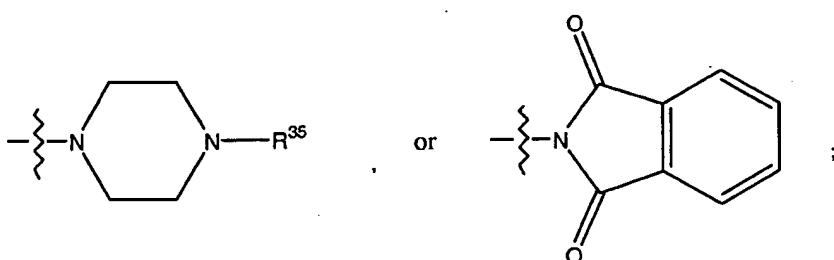
20 R³⁰ represents SO₂N(R¹⁰)₂, H, NHOH, amidino, or C(=NH)CH₃;

R³¹ represents R³⁰, amino-amidino, NH-C(=NH)CH₃, or R¹⁰;

R³² represents H, C(O)-CH₂-NH₂, or C(O)-CH(CH(CH₃)₂)-NH₂;

25 R³³ and R³⁴ independently at each occurrence represent R¹⁰, (CH₂)₀₋₄-Ar, optionally substituted aryl, (CH₂)₀₋₄ optionally substituted heteroaryl, (CH₂)₁₋₄-CN, (CH₂)₁₋₄-N(R¹⁰)₂, (CH₂)₁₋₄-OH, (CH₂)₁₋₄-SO₂-N(R¹⁰)₂;

alternatively, R³³ and R³⁴ along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-isouquinoline,



30 R³⁵ represents R¹⁰, SO₂-R¹⁰, COR¹⁰, or CONHR¹⁰;

E represents a bond, S(O)₀₋₂, O or NR¹⁰;

W₁, W₂, W₃ and W₄ independently represent C or N; and

Q , Q^1 , Q^2 , Q^3 , L^1 , L^2 , L^3 and L^4 independently at each occurrence represent N-natural or unnatural amino acid side chain, CHR^{10} , O, NH, S(O)_{0-2} , N-C(O)-NHR^{10} , $\text{SO}_2\text{-N(R}^{10}\text{)}_2$, $\text{N-C(O)-NH-}(\text{CH}_2)_{1-4}\text{-R}^{26}$, NR^{10} , N-heteroaryl, N-C(=NH)-NHR^{10} , or N-C(=NH)C_{1-4} alkyl;

R^{26} represents OH, NH_2 , or SH;

provided that, (i) when $R^1 = \text{OH}$; $R^7 = \text{amidine}$; R^2 , R^6 , R^8 , R^9 , and R^{20} each represent H; and R^3 , R^4 , R^5 are independently chosen from H, CH_3 , and halogen, then only one of R^3 , R^4 , and R^5 represents H; (ii) when $R^1 = \text{OH}$; $R^7 = \text{amidine}$; R^2 , R^3 , R^4 , R^5 , and R^{20} each represent H; and R^6 , R^8 , R^9 are independently chosen from H, CH_3 , and halogen, then only one of R^6 , R^8 , and R^9 represents H; (iii) at least two of W_1 , W_2 , W_3 and W_4 represent C and at least one of W_1 , W_2 , W_3 and W_4 represent N; and (iv) when $R^1 = \text{OH}$; $R^7 = \text{amidine}$; and R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , and R^9 , represent H, R^{20} cannot be CH_3 .

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2. A compound of Formula I:

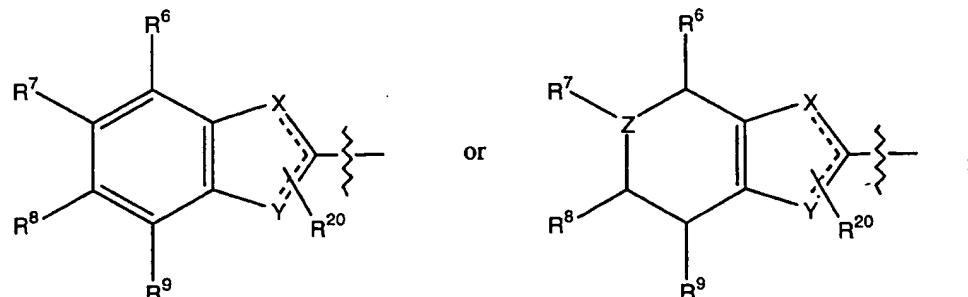
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A-B

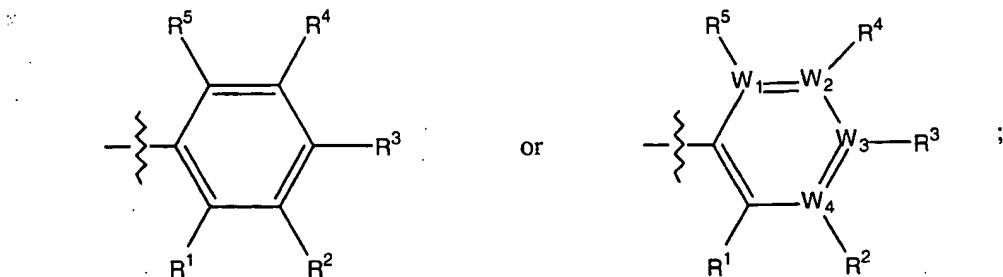
its prodrug forms, or pharmaceutically acceptable salts thereof, wherein

A represents

25



B represents

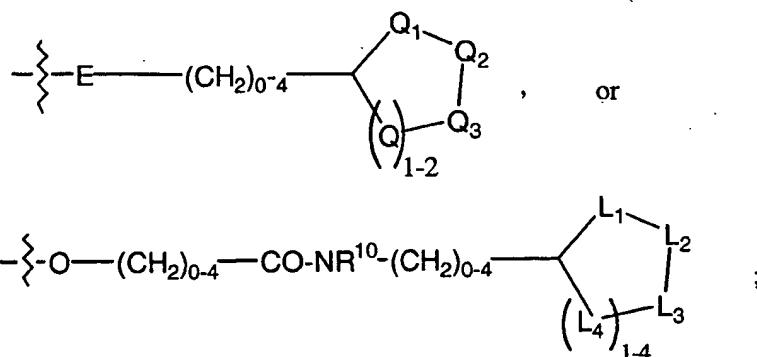


R^1 represents OH, halogen, COOH, COO-C_{1-4} alkyl, $O-(\text{CH}_2)_{0-1}-\text{Ph}$, $N(\text{R}^{10})_2$, $\text{CH}_2\text{OR}^{10}$, C_{1-6} halogenated alkyl, $O-(\text{CH}_2)_{1-4}-\text{CO-N}(\text{R}^{10})_2$,

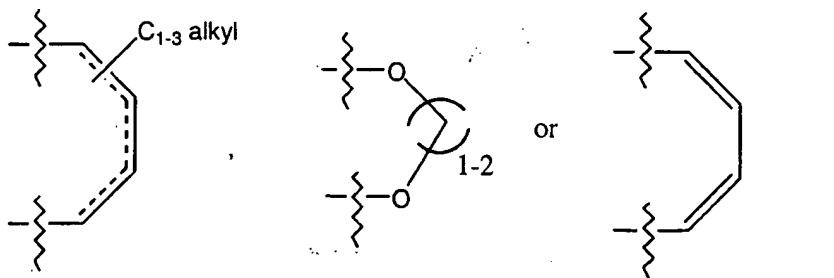
5 SC_{1-4} alkyl, $\text{NHSO}_2\text{C}_{1-4}$ alkyl, SO_2-OH , $O-\text{SO}_2-\text{OH}$, $O-\text{SO}_2-\text{O-C}_{1-4}$ alkyl, OP(O)(OH)_2 , or $\text{OPO}_3\text{C}_{1-4}$ alkyl;

10 R^2 , R^3 , R^4 , and R^5 independently at each occurrence represent H, SH, OR^{10} , halogen, COOR^{10} , $\text{CONR}^{11}\text{R}^{12}$, optionally substituted aryl, optionally substituted heterocyclyl, C_{4-14} cycloalkyl-
 C_{1-4} alkyl, C_{1-4} alkyl aryl, optionally substituted C_{1-14} straight chain, branched or cyclo alkyl, $O-(\text{CH}_2)_{2-6}-\text{NR}^{10}-$
 $(\text{CH}_2)_{0-3}-\text{R}^{24}$, $\text{NR}^{10}\text{R}^{24}$, $(\text{CH}_2)_{1-4}-\text{NR}^{33}\text{R}^{34}$, $(\text{CH}_2)_{1-4}-\text{COOR}^{33}$, $O-(\text{CH}_2)_{1-3}-\text{CO-}$ het, $O-(\text{CH}_2)_{1-2}-\text{NH-CO-aryl}$, $O-(\text{CH}_2)_{1-2}-\text{NR}^{10}-\text{CO-NR}^{10}\text{R}^{33}$, $O-(\text{CH}_2)_{0-2}-$
15 $\text{C}(\text{O})-\text{NR}^{33}\text{R}^{34}$, $O-(\text{CH}_2)_{1-4}-\text{COOR}^{10}$, $O-(\text{CH}_2)_{1-3}-\text{het-R}^{32}$, O-optionally substituted cycloalkyl, $O-(\text{CH}_2)_{1-4}-\text{NR}^{10}-\text{COO-t-butyl}$, $O-(\text{CH}_2)_{1-4}-$
 $\text{NR}^{10}\text{R}^{33}$, $O-(\text{CH}_2)_{1-4}-\text{NR}^{10}-\text{C}(\text{O})-\text{C}_{0-3}$ -alkyl-optionally substituted aryl, O-substituted cycloalkyl, $O-(\text{CH}_2)_{0-6}$ -optionally substituted aryl, $(\text{CH}_2)_{1-4}-\text{NH-C}(\text{O})\text{O}-(\text{CH}_2)_{1-4}-\text{PhR}^{13}\text{R}^{14}$, NO_2 , $O-(\text{CH}_2)_{0-4}-\text{C}(\text{O})-\text{NH-tetrahydro carboline}$, $\text{NR}^{10}\text{R}^{28}$, $O-(\text{CH}_2)_{1-3}-$

20 optionally substituted het, $\text{CH}_2\text{COOCH}_3$, $\text{CH}=\text{CH-COOCH}_3$, 5-amidino benzimidazole,



alternatively R^2 and R^3 taken together form



R⁶ and R⁹ independently at each occurrence represents H, halogen, cyano, C₁₋₄ alkyl, C₁₋₄ halogenated alkyl, NO₂, O-aryl or OR¹¹;

R⁷ and R⁸ independently at each occurrence represent OH, CF₃, H, NO₂, C₁₋₄ alkyl, OC₁₋₄ alkyl, or O-aryl, halogen, cyano, or a basic group selected from guanidino, C(=NH)N(R¹⁰)₂, C(=NH)-NH-NH₂, C(=O)NH₂, 2-imidazoline, N-amidinomorpholine, N-amidino piperidine, 4-hydroxy-N-amidino piperidine, N-amidino pyrrolidine, tetrahydro pyrimidine, and thiazolidin-3-yl-methylideneamine; with the proviso that only one of R⁷ and R⁸ represent a basic group;

R¹⁰ independently at each occurrence represents H, (CH₂)₀₋₂-aryl, C₁₋₄ halo alkyl, or C₁₋₁₄ straight chain, branched or cyclo alkyl, and alternatively, when one atom is substituted with two R¹⁰ groups, the atom along with the R¹⁰ groups can form a five to 10 membered ring structure;

R¹¹ and R¹² independently at each occurrence represent H or C₁₋₄ alkyl;

R²⁰ represents R²⁴, C₁₋₄-alkyl, (CH₂)₁₋₃-biphenyl, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl)₂, (CH₂)₁₋₄-NH-C(O)-R²⁴, (CH₂)₁₋₄-NH-SO₂-R²⁴, halogen, COOR¹⁰, (CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂-alkyl), (CH₂)₁₋₄-NR¹⁰-C(O)-R²⁴, (CH₂)₁₋₄-NR¹⁰-SO₂-R²⁴, (CH₂)₁₋₄-het, (CH₂)₁₋₄-CON(R¹⁰)₂, (CH₂)₁₋₄-N(R¹⁰)-C(O)-NR¹⁰R²⁴, (CH₂)₁₋₄-N(R¹⁰)-C(S)-NR¹⁰R²⁴, or (CH₂)₁₋₃-COOH;

R²⁴ represents R¹⁰, (CH₂)₁₋₄-optionally substituted aryl, (CH₂)₀₋₄OR¹⁰, CO-(CH₂)₁₋₂-N(R¹⁰)₂, CO(CH₂)₁₋₄-OR¹⁰, (CH₂)₁₋₄-COOR¹⁰, (CH₂)₀₋₄-N(R¹⁰)₂, SO₂R¹⁰, COR¹⁰, CON(R¹⁰)₂, (CH₂)₀₋₄-aryl-COOR¹⁰, (CH₂)₀₋₄-aryl-N(R¹⁰)₂, or (CH₂)₁₋₄-het-aryl;

R²⁸ represents (CH₂)₁₋₂-Ph-O-(CH₂)₀₋₂-het-R³⁰, C(O)-het, CH₂-Ph-CH₂-het-(R³⁰)₁₋₃; (CH₂)₁₋₄-cyclohexyl-R³¹, CH₂-Ph-O-Ph-(R³⁰)₁₋₂,

$\text{CH}_2\text{-}(\text{CH}_2\text{OH})\text{-het-R}^{30}$, $\text{CH}_2\text{-Ph-O-cycloalkyl-R}^{31}$, $\text{CH}_2\text{-het-C(O)-CH}_2\text{-het-R}^{30}$, or $\text{CH}_2\text{-Ph-O-(CH}_2\text{)-O-het-R}^{30}$;

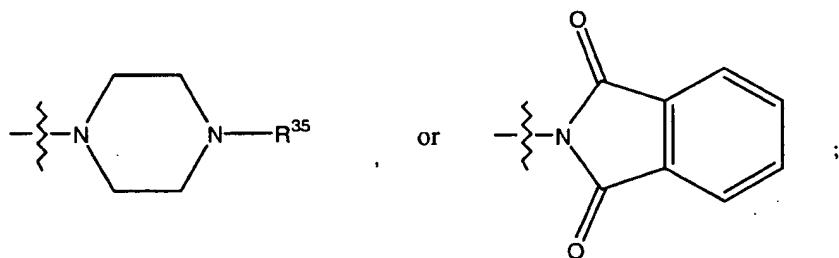
R^{30} represents $\text{SO}_2\text{N(R}^{10}\text{)}_2$, H, NHOH, amidino, or C(=NH)CH_3 ;

R^{31} represents R^{30} , amino-amidino, NH-C(=NH)CH_3 or R^{10} ;

5 R^{32} represents H, $\text{C(O)-CH}_2\text{-NH}_2$, or $\text{C(O)-CH(CH(CH}_3\text{)}_2\text{-NH}_2$;

R^{33} and R^{34} independently at each occurrence represent R^{10} , $(\text{CH}_2)_{0-4}\text{-Ar}$, optionally substituted aryl, $(\text{CH}_2)_{0-4}$ optionally substituted heteroaryl, $(\text{CH}_2)_{1-4}\text{-CN}$, $(\text{CH}_2)_{1-4}\text{-N(R}^{10}\text{)}_2$, $(\text{CH}_2)_{1-4}\text{-OH}$, $(\text{CH}_2)_{1-4}\text{-SO}_2\text{-N(R}^{10}\text{)}_2$;

10 alternatively, R^{33} and R^{34} along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-isouquinoline,



15

R^{35} represents R^{10} , $\text{SO}_2\text{-R}^{10}$, COR^{10} , or CONHR^{10} ;

E represents a bond, S(O)_{0-2} , O or NR^{10} ;

W_1 , W_2 , W_3 and W_4 independently represent C or N; and

20 Q, Q^1 , Q^2 , Q^3 , L^1 , L^2 , L^3 and L^4 independently at each occurrence represent N-natural or unnatural amino acid side chain, CHR^{10} , O, NH, S(O)_{0-2} , N-C(O)-NHR^{10} , $\text{SO}_2\text{-N(R}^{10}\text{)}_2$, $\text{N-C(O)-NH-}(\text{CH}_2)_{1-4}\text{-R}^{26}$, NR^{10} , N-heteroaryl, N-C(=NH)-NHR^{10} , or N-C(=NH)C_{1-4} alkyl;

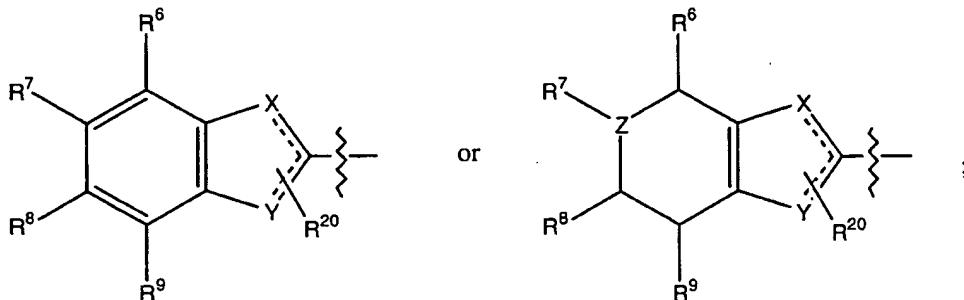
25 R^{26} represents OH, NH₂, or SH;

provided that, (i) when $R^1 = \text{OH}$; $R^7 = \text{amidine}$; R^2 , R^6 , R^8 , R^9 , and R^{20} each represent H; and R^3 , R^4 , R^5 are independently chosen from H, CH₃, and halogen, then only one of R^3 , R^4 , and R^5 represents H; (ii) when $R^1 = \text{OH}$; $R^7 = \text{amidine}$; R^2 , R^3 , R^4 , R^5 , and R^{20} each represent H; and R^6 , R^8 , R^9 are independently chosen from H, CH₃, and halogen, then only one of R^6 , R^8 , and R^9 represents H; (iii) at least two of

30 R^6 , R^8 , and R^9 are independently chosen from H, CH₃, and halogen, then only one of R^6 , R^8 , and R^9 represents H;

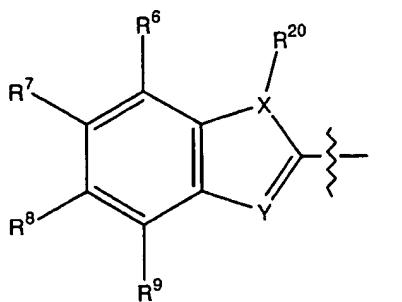
W_1 , W_2 , W_3 , and W_4 represent C and at least one of W_1 , W_2 , W_3 , and W_4 represent N; and (iv) when R^1 = OH; R^7 = amidine; and R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , and R^9 , represent H, R^{20} cannot be CH_3 .

5 3. A compound of Claim 2 wherein
A represents



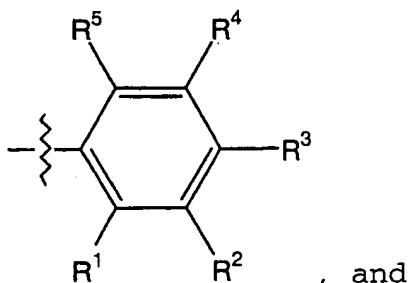
10 R^1 represents OH, O-Ph, COOH, or $P(O)(OH)_2$;
 R^7 represents H, Br, $CONH_2$, CN, $C(=NH)-NH-NH_2$, $NH-C(=NH)-NH$, or $C(=NH)-NH_2$;
 R^{20} represents H, C_{1-2} alkyl, $(CH_2)_{1-4}$ -optionally substituted 15 aryl, $(CH_2)_{1-4}$ -het; $(CH_2)_{1-4}-N(R^{10})_2$, $(CH_2)_{1-4}-CON(R^{10})_2$, $(CH_2)_{1-4}-NR^{10}-C(O)-R^{24}$, $(CH_2)_{1-4}-NR^{10}-SO_2-R^{24}$, or $(CH_2)_{1-3}-COOH$;
X and Y independently at each occurrence are selected from NH, N, C, or CH, such that at least one of X and Y always represents N or NH ; and
20 Z represents C or N;
provided that, (i) when Z represents N, R^7 represents H or $C(=NH)NH_2$.

4. A compound of claim 3 wherein
25 A represents



and

B represents



, and

5

X and Y represent N; and

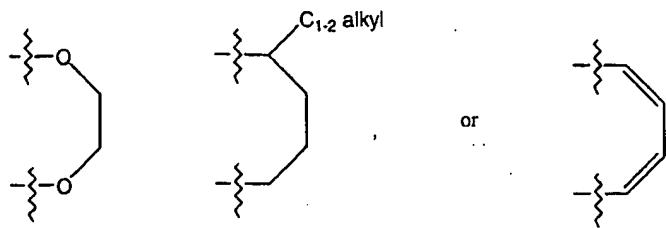
R' represents -CONH₂, or C(=NH)-NH₂;

5. A compound of claim 4 wherein

10 R¹ represents OH, -COOH, and O-P(O)(OH)₂;

R² and R³ independently represent halogen, H, C₁₋₄ alkyl, Ph, toluyl, OH, O-(CH₂)₁₋₃-C(O)-NH-(CH₂)₁₋₂-CN, O-(CH₂)₁₋₃-Ph-p-OCH₃, O-CH₂-C(O)-NH-(CH₂)₁₋₂-CH-(CH₃)₂, O-CH₂-C(O)-NH-(CH₂)-Ph, O-CH₂-C(O)-NH-(CH₂)-Ph-pCH₃, O-C₁₋₃ alkyl, O-(CH₂)₀₋₂-Ph-R¹⁰, O-CH₂-C(O)-NH-(CH₂)₂-H, Ph-C₁₋₃ alkyl, Ph-N(R¹⁰)₂, O-(CH₂)₁₋₃-het, O-(CH₂)₁₋₃-Ph-halo, O-(CH₂)₁₋₃-NHSO₂Ph-R¹⁰, O-(CH₂)₁₋₃-NHCO-(CH₂)₀₋₂-Ph, O-CH₂-C(O)-NH-CH₂-COO-C(CH₃)₃, O-(CH₂)₂-NHC(O)-CH₂-NH₂, -OPh, O-(CH₂)₁₋₃-NH-het, O-(CH₂)₂-NH-C(O)-pyridyl, O-(CH₂)₂-NH-C(O)-NH-benzyl, O-(CH₂)₂-cyclohexyl, O-(CH₂)₂-NH-C(O)-CONH₂, O-(CH₂)₂-NH-C(O)-CH₂-OCH₃, thiophene, pyridyl, or O-(CH₂)₂-pyridyl;

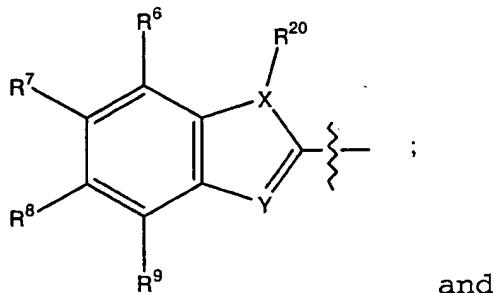
alternatively R² and R³ taken together form



R⁴ represents halogen, H, NO₂, C₁₋₂-alkyl, CH=CH-COOCH₃, NHSO₂C₁₋₂ alkyl, NHCO-het, (CH₂)₁₋₃-COOR¹⁰, (CH₂)₁₋₃-CONH-(CH₂)₁₋₃-pyridyl, or (CH₂)₁₋₃-CONH-(CH₂)₁₋₃-dichlorophenyl;
 5 R⁵ represents H;
 R⁶ represents H;
 R⁷ represents C(=NH)-NH₂ or NH(=NH)NH₂;
 R⁸ represents H, halogen, OR¹⁰, CF₃, or C(=NH)-NH₂;
 10 R⁹ represents H or halogen; and
 R²⁰ represents H.

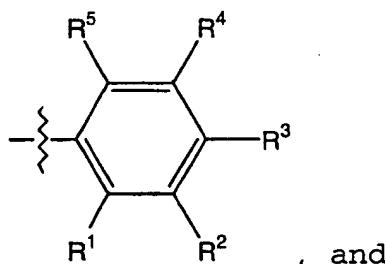
6. A compound of claim 2 wherein
 A represents

15



and

B represents

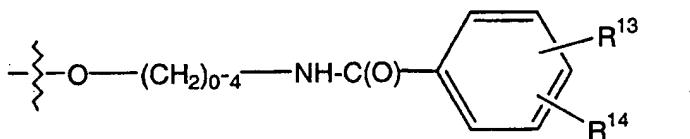
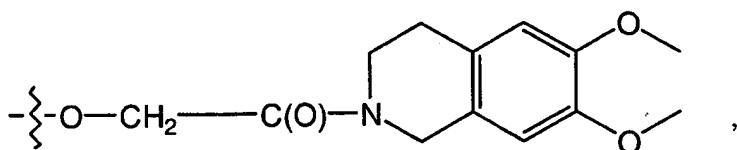


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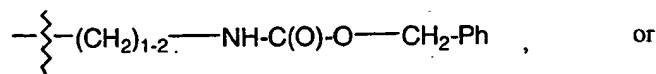
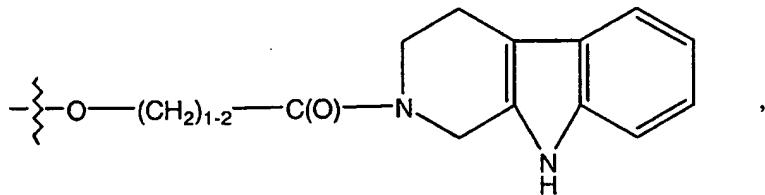
, and

X and Y represent N.

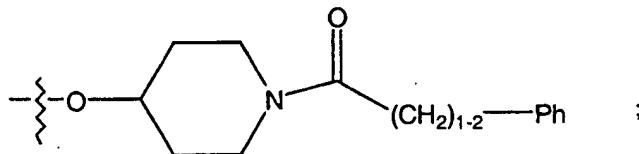
7. A compound of claim 6 wherein
 R^1 represents OH, or COOH;
 R^2 represents H, halogen, OH, phenyl, $O-(CH_2)_{1-3}-Ph$,
5 imidazolyl, 5-amidino benzimidazolyl, $O-(CH_2)_{1-2}-C(O)-NH-C_{1-6}$
alkyl, or $O-CH_2-C(O)-NH-CH_2-Ph$;
 R^3 represents H, $O-CH_2-COOH$, $O-CH_2-C(O)O-C_2H_5$, $O-CH_2-C(O)-NH-$
 $(CH_2)_{1-4}-aryl$, $O-(CH_2)_{1-4}-NH-C(O)-naphthyl$, CONH₂, $O-(CH_2)_{1-2}-$
 $C(O)N(R^{10})-(CH_2)_{1-3}-Ph-R^{13}R^{14}$, $O-CH_2-C(O)-N(R^{10})-CH_2-piperanyl$, $O-$
10 $CH_2-C(O)-NH-CH_2-indoyl$, $(CH_2)_{0-4}-aryl$,



15

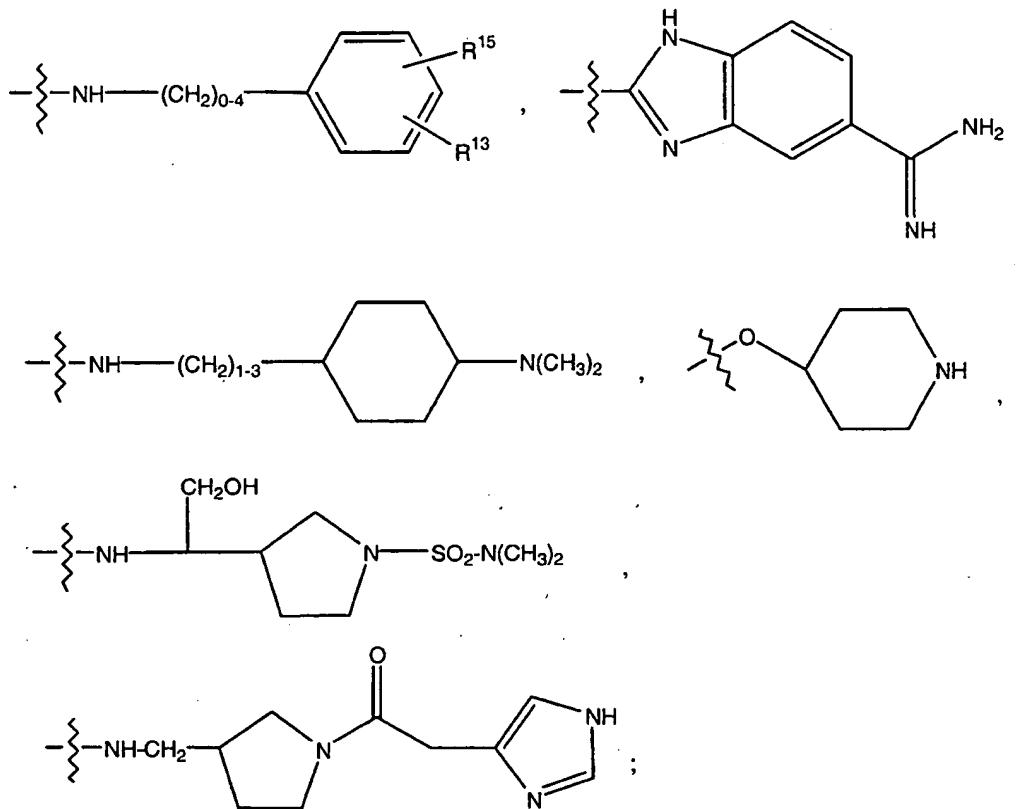


or



R^4 represents H, -CH₃, halogen, -OCH₃, $-(CH_2)_{1-2}COOR^{10}$, -COOH, -NO₂, -OH, aryl,

20



R⁵ represents H;

R⁶ represents H;

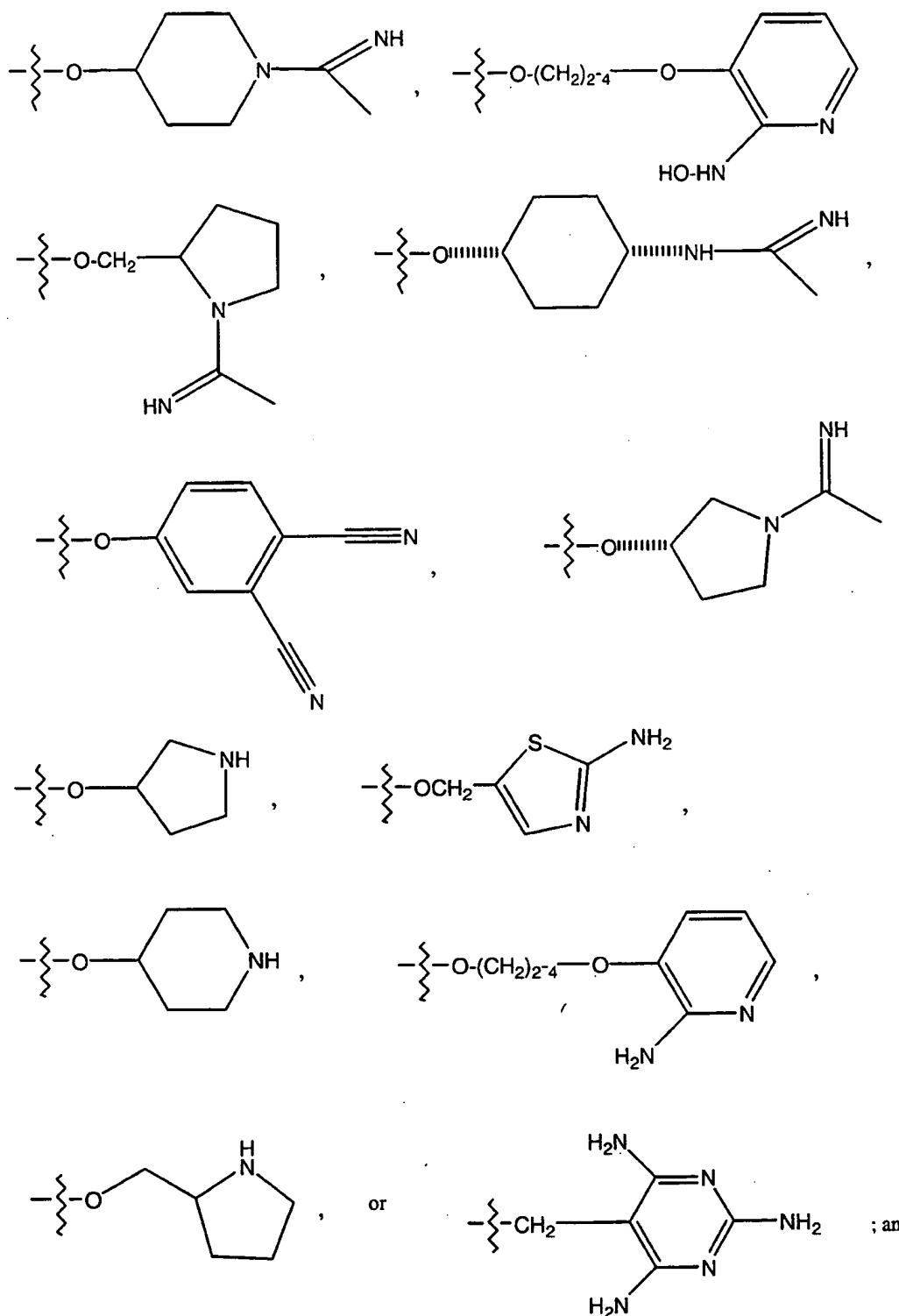
5 R⁷ represents H, halogen, -C(O)-NH₂, -C(=NH)-NH₂;

R⁸ represents H, Cl, F, OH or OCH₃;

R⁹ represents H;

R¹³ and R¹⁴ independently at each occurrence represents H, halogen, -OC₁₋₂ alkyl, -OH, -CF₃, or -C₁₋₄ alkyl; and

10 R¹⁵ represents H,



R^{20} represents H or $-CH_2-Ph$.

5 8. A compound of claim 2, wherein the compound is selected from

3-[3-Bromo-5-(6-carbamimidoyl-1H-benzimidazol-2-yl)-4-hydroxy-phenyl]-N-phenethyl-propionamide;

3-[4-(6-Carbamimidoyl-1H-benzimidazol-2-yl)-3-hydroxy-phenyl]-N-(2,3-dichloro-benzyl)-propionamide;

5 2-[4-(6-Carbamimidoyl-1H-benzimidazol-2-yl)-3-hydroxy-phenoxy]-N-(2,3-dichloro-benzyl)-acetamide;

3-[3-Bromo-5-(6-carbamimidoyl-1H-benzimidazol-2-yl)-4-hydroxy-phenyl]-N-[2-(2,4-dichloro-phenyl)-ethyl]-propionamide;

10 3-[3-Bromo-5-(6-carbamimidoyl-1H-benzimidazol-2-yl)-4-hydroxy-phenyl]-N-(2-pyridin-2-yl-ethyl)-propionamide;

3-[3-Bromo-5-(6-carbamimidoyl-1H-benzimidazol-2-yl)-4-hydroxy-phenyl]-N-(3-phenyl-propyl)-propionamide;

15 2-[4-(6-Carbamimidoyl-1H-benzimidazol-2-yl)-3-hydroxy-phenoxy]-N-naphthalen-1-ylmethyl-acetamide;

2-(3'-Amino-5-chloro-2-hydroxy-biphenyl-3-yl)-3H-benzimidazole-5-carboxamidine;

3-[3-Bromo-5-(6-carbamimidoyl-1H-benzimidazol-2-yl)-4-hydroxy-phenyl]-propionic acid;

20 2-(3,5-Bis-hydroperoxy-2-hydroxy-phenyl)-3H-benzimidazole-5-carboxamidine;

2-[4-(5-Carbamimidoyl-1H-benzimidazol-2-yl)-3-hydroxy-phenoxy]-N-(3-chloro-benzyl)-acetamide;

N-Benzyl-3-[3-bromo-5-(6-carbamimidoyl-1H-benzimidazol-2-yl)-4-hydroxy-phenyl]-propionamide;

25 2-(3,5-Dibromo-2,4-dihydroxy-phenyl)-3H-benzimidazole-5-carboxamidine;

2-(2-Hydroxy-biphenyl-3-yl)-3H-benzimidazole-5-carboxamidine;

30 2-(5-Chloro-2-hydroxy-biphenyl-3-yl)-3H-benzimidazole-5-carboxamidine;

2-(2-Hydroxy-3-phenethyloxy-phenyl)-3H-benzimidazole-5-carboxamidine;

N-(3-Bromo-benzyl)-2-[4-(5-carbamimidoyl-1H-benzimidazol-2-yl)-3-hydroxy-phenoxy]-acetamide;

35 2-{3-[1-(3-Amino-propionyl)-pyrrolidin-2-ylmethoxy]-2-hydroxy-phenyl}-3H-benzimidazole-5-carboxamidine;

2-(5-Chloro-2-hydroxy-3-pyridin-3-yl-phenyl)-1H-
benzimidazole-5-carboxamidine;
2-[3-(5-Carbamimidoyl-1H-benzimidazol-2-yl)-2-hydroxy-
phenyl]-3,4,6,7-tetrahydro-imidazo[4,5-c]pyridine-5-
5 carboxamidine;
2-[3-(1-Aminoacetyl-pyrrolidin-2-ylmethoxy)-2-hydroxy-
phenyl]-3H-benzimidazole-5-carboxamidine; and
2-(2-Hydroxy-3-phenoxy-phenyl)-3H-benzimidazole-5-
carboxamidine;

10 2-[2-Hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-phenyl]-1H-
benzimidazole-5-carboxamidine;
2-[3-(1-Aminoacetyl-piperidin-3-ylmethoxy)-2-hydroxy-
phenyl]-1H-benzimidazole-5-carboxamidine;
2-{3-[1-(2-Amino-3-methyl-butyryl)-pyrrolidin-2-ylmethoxy]-
15 2-hydroxy-phenyl}-1H-benzimidazole-5-carboxamidine;
2-[2-Hydroxy-3-(1-hydroxyacetyl-pyrrolidin-2-ylmethoxy)-
phenyl]-1H-benzimidazole-5-carboxamidine;
2-(2-Hydroxy-5-iodo-3-methoxy-phenyl)-1H-benzimidazole-5-
carboxamidine;

20 2-{3-[1-(2-Amino-3-methyl-butyryl)-pyrrolidin-2-ylmethoxy]-
2-hydroxy-phenyl}-3H-benzimidazole-5-carboxamidine;
2-(2-Hydroxy-5-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-
benzylamino}-phenyl)-3H-benzimidazole-5-carboxamidine;
compound with methane;

25 2-(2-Hydroxy-5-{4-[1-(1-imino-ethyl)-piperidin-3-
ylmethoxy]-benzylamino}-phenyl)-3H-benzimidazole-5-
carboxamidine;
2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-3H-benzimidazole-5-
carboxamidine;

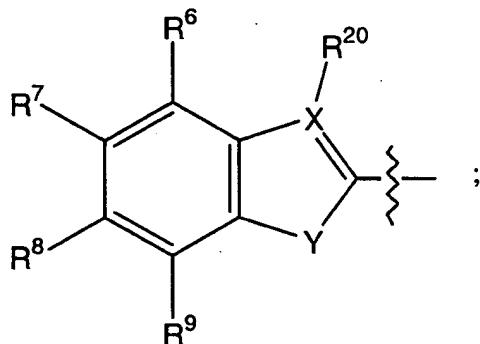
30 3-[2,6-Dibromo-4-(6-carbamimidoyl-1H-benzimidazol-2-yl)-3-
hydroxy-phenoxy]-propionic acid;
3-[2,6-Dibromo-4-(6-carbamimidoyl-1H-benzimidazol-2-yl)-3-
hydroxy-phenoxy]-propionic acid ethyl ester; and
2-[3-Bromo-2-hydroxy-5-(3-methoxy-but-3-enyl)-phenyl]-3H-
35 benzimidazole-5-carboxamidine;
or a stereoisomer or pharmaceutically acceptable salt form
thereof.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 2 or a pharmaceutically acceptable salt thereof.

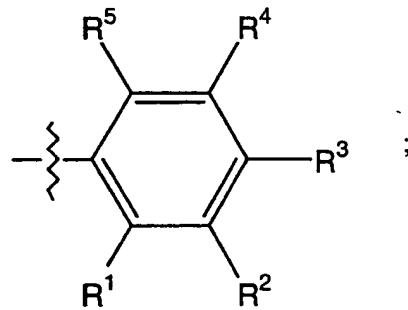
11. A method for treating or preventing a thromboembolic disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to Claim 2 or a pharmaceutically acceptable salt thereof.

12. A compound of Claim 2 wherein A represents



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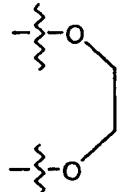
B represents



X represents C; and

Y represents NH.

13. A compound of claim 12 wherein
 R¹ represents -OH, -COOH, or P(O)(OH)₂;
 R² represents H, halogen, R¹⁰, -aryl, heteroaryl, -C₁₋₂-alkyl,
 5 COOH, -OC₁₋₂-alkyl, -O-(CH₂)₀₋₂-aryl, or -C₆₋₁₀ aryl-C₁₋₄ alkyl;
 R³ represents H or -O-(CH₂)₁₋₃-COOH;
 alternatively R² and R³ taken together represent



R⁴ represents H, -C₁₋₄ alkyl, -(CH₂)₁₋₄-COOH, -(CH₂)₁₋₄-COOC₁₋₂-
 10 alkyl, halogen, -(CH₂)₁₋₂-CONH₂, -CONH₂, -NO₂, -O-C₁₋₂ alkyl, or
 -OH;
 R⁵ represents H, -C₁₋₃ alkyl, -(CH₂)₁₋₄-C(O)-NH-(CH₂)₁₋₃-
 heteroaryl, -(CH₂)₁₋₄-C(O)-NH-CH₃, or -COOH;
 R⁶ represents H, halogen, or -C₁₋₃ alkyl;
 15 R⁷ represents -C(O)-NH₂, -C(=NH)-NH-NH₂, or amidino;
 R⁸ represents H, or halogen; and
 R²⁰ represents H, -(CH₂)₁₋₄-Ph-N(SO₂-C₁₋₂alkyl), -(CH₂)₁₋₄-NR¹⁰-
 C(O)-R²⁴, -(CH₂)₁₋₄-NR¹⁰-SO₂-R²⁴, -(CH₂)₁₋₄-het, -(CH₂)₁₋₄-CON(R¹⁰)₂,
 - (CH₂)₁₋₄-N(R¹⁰)-C(O)-NR¹⁰R²⁴, -(CH₂)₁₋₂-Ph-NH₂, -(CH₂)₁₋₂-Ph-NO₂,
 20 -(CH₂)₁₋₄-N(R¹⁰)-C(S)-NR¹⁰R²⁴, -C₁₋₂-alkyl, -(CH₂)₁₋₄-optionally
 substituted aryl, -(CH₂)₁₋₄-het; -(CH₂)₁₋₃-N(R¹⁰)₂; -(CH₂)₁₋₄-
 CON(R¹⁰)₂, or -(CH₂)₁₋₃-COOH.

14. A compound of claim 13 wherein the compound is
 25 selected from
 3-Benzyl-2-(3-chloro-2-hydroxy-phenyl)-1H-indole-5-
 carboxamidine;
 3-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-
 hydroxy-phenyl]-propionic acid;
 30 [3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-
 hydroxy-phenyl]-acetic acid;
 6-Chloro-2-(3,5-dichloro-2-hydroxy-phenyl)-1H-indole-5-
 carboxamidine;

3-Bromo-5-(5-carbamimidoyl-1H-indol-2-yl)-4-hydroxy-benzamide;

2-(3,5-Dichloro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;

5 3-(4-Amino-benzyl)-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;

2-(2-Hydroxy-biphenyl-3-yl)-1H-indole-5-carboxamidine;

2-(3-Bromo-2-hydroxy-5-nitro-phenyl)-1H-indole-5-carboxamidine;

10 2-(5-Hydroxy-2,3-dihydro-benzo[1,4]dioxin-6-yl)-1H-indole-5-carboxamidine;

3-Benzyl-2-(2-hydroxy-phenyl)-1H-indole-5-carboxamidine;

3-Benzyl-2-(3,5-difluoro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;

15 3-Benzyl-2-(3,5-dibromo-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;

[3-Bromo-5-(5-carbamimidoyl-1H-indol-2-yl)-4-hydroxy-phenyl]-acetic acid;

3-Benzyl-2-(5-chloro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;

20 2-[3-Bromo-5-(5-carbamimidoyl-1H-indol-2-yl)-4-hydroxy-phenyl]-acetamide;

2-(3,5-Difluoro-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;

25 2-(3,5-Dibromo-2-hydroxy-phenyl)-1H-indole-5-carboxamidine;

2-(2-Hydroxy-5-methyl-biphenyl-3-yl)-1H-indole-5-carboxamidine;

2-(2-Hydroxy-5,4'-dimethyl-biphenyl-3-yl)-1H-indole-5-carboxamidine;

30 2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;

3-Benzyl-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;

3-Benzyl-2-(3-chloro-2-hydroxy-5-methyl-phenyl)-1H-indole-

35 5-carboxamidine;

3-Benzyl-2-(2-hydroxy-3,5-dimethyl-phenyl)-1H-indole-5-carboxamidine;

2-(3,5-Dibromo-2-hydroxy-phenyl)-3-methyl-1H-indole-5-carboxamidine;

2-(2-Hydroxy-5-methyl-3-thiophen-2-yl-phenyl)-1H-indole-5-carboxamidine;

5 2-[2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-5-carbamimidoyl-1H-indol-3-yl]-acetamide;
[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-acetic acid methyl ester;

10 3-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-propionic acid methyl ester;

3-(3-Amino-benzyl)-2-(3-bromo-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;

15 2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-3-(3-nitro-benzyl)-1H-indole-5-carboxamidine;

3-(3-Amino-benzyl)-2-(2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;

3-Benzyl-2-(3-chloro-2-hydroxy-5-methyl-phenyl)-1H-indole-5-carboxamidine;

20 6-Chloro-2-{5-[2-(1,1-dioxo-1-thiomorpholin-4-yl)-2-oxo-ethyl]-2-hydroxy-biphenyl-3-yl}-1H-indole-5-carboxamidine;

2-[5-(5-Carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-biphenyl-3-yl]-N-(2-piperidin-1-yl-ethyl)-acetamide;

25 6-Chloro-2-{2-hydroxy-5-[2-(2-methoxymethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-biphenyl-3-yl}-1H-indole-5-carboxamidine;

6-Chloro-2-{2-hydroxy-5-[2-oxo-3-(tetrahydro-furan-2-yl)-propyl]-biphenyl-3-yl}-1H-indole-5-carboxamidine;

30 2-[5-(5-Carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-biphenyl-3-yl]-N-(tetrahydro-furan-2-ylmethyl)-acetamide;

2-[5-(5-Carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-biphenyl-3-yl]-N-(3-methoxy-propyl)-acetamide;

Morpholine-4-carboxylic acid {2-[5-(5-carbamimidoyl-6-chloro-1H-indol-2-yl)-6-hydroxy-biphenyl-3-yloxy]-ethyl}-amide;

35 Phosphoric acid mono-{2-[3-(3-benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-ethyl} ester;

2-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-N-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-phenyl}-acetamide;

5 4-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-butyric acid;

2-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-acetamide;

2-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-N,N-dimethyl-acetamide;

10 [3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-acetic acid;

3-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-pentanedioic acid bis-[(2-morpholin-4-yl-ethyl)-amide];

15 3-[3-(3-Benzyl-5-carbamimidoyl-1H-indol-2-yl)-5-bromo-4-hydroxy-phenyl]-propionamide; and

2-(3-Bromo-2-hydroxy-5-methyl-phenyl)-3-(4-nitro-benzyl)-1H-indole-5-carboxamidine;

or a stereoisomer or pharmaceutically acceptable salt form
20 thereof.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 12 or a pharmaceutically acceptable salt thereof.

16. A method for treating or preventing a thromboembolic disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a compound
30 according to Claim 12 or a pharmaceutically acceptable salt thereof.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 235/18, A61K 31/415, A61P 7/02, (continued on the following page)		A3	(11) International Publication Number: WO 00/35886 (43) International Publication Date: 22 June 2000 (22.06.00)		
(21) International Application Number: PCT/US99/30302		Wendy, B. [US/US]; 110 West 3rd Avenue #5, San Mateo, CA 94403 (US).			
(22) International Filing Date: 17 December 1999 (17.12.99)		(74) Agents: KATHARDEKAR, Vinit, G. et al.; Axys Pharmaceuticals, Inc., 180 Kimball Way, South San Francisco, CA 94080 (US).			
(30) Priority Data: 60/113,007 18 December 1998 (18.12.98) US		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).			
(71) Applicant (for all designated States except US): AXYS PHARMACEUTICALS, INC. [US/US]; 180 Kimball Way, South San Francisco, CA 94080 (US).		Published <i>With international search report.</i>			
(72) Inventors; and (75) Inventors/Applicants (for US only): ALLEN, Darin, Arthur [US/US]; 519 Sierra Vista #3, Mountain View, CA 94043 (US); HATAYE, Jason, M. [US/US]; 574 Holyoke, San Francisco, CA 94134-1737 (US). HRUZEWCZ, Witold, N. [PL/US]; 1503 McKinnon Avenue, San Francisco, CA 94124 (US). KOLESNIKOV, Aleksandr [UA/US]; 1474 46th Avenue, San Francisco, CA 94122 (US). MACKMAN, Richard, Laurence [GB/US]; 2240 Bay Street, Apt. 302, San Francisco, CA 94403 (US). RAI, Roopa [IN/US]; 237 Clifton Avenue, San Carlos, CA 94070 (US). SPENCER, Jeffrey, R. [US/US]; 8 Baycrest Way, South San Francisco, CA 94080 (US). VERNER, Erik, J. [US/US]; 709 Catamaran Street, #1, Foster City, CA 94404 (US). YOUNG,		(88) Date of publication of the international search report: 26 October 2000 (26.10.00)			
(54) Title: (HETERO)ARYL-BICYCLIC HETEROARYL DERIVATIVES, THEIR PREPARATION AND THEIR USE AS PROTEASE INHIBITORS					
(57) Abstract					
<p>The present invention provides novel compounds of the Formula (I): A-B, its prodrug forms, or pharmaceutically acceptable salts thereof, wherein A represents a saturated, unsaturated, or a partially unsaturated bicyclic heterocyclic ring structure, and B represents an aryl or a heteroaryl group. Preferred compounds of the present invention comprise a benzimidazole or indole nucleus. The compounds of this invention are inhibitors of serine proteases, Urokinase (uPA), Factor Xa (FXa), and/or Factor VIIa (FVIIa), and have utility as anti-cancer agents and/or as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals.</p>					

(S1) International Patent Classification:⁷ (continued)

C07D 401/10, 403/10, 471/04, 417/10, 413/10, 407/10, 209/12, 409/10, 407/12, A61K 31/44, 31/425, 31/40,
C07F 9/09, A61K 31/66 // (C07D 471/04, 235:00, 221:00)

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/30302

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07D235/18	A61K31/415	A61P7/02	C07D401/10	A61K31/44
	C07D403/10	C07D471/04	C07D417/10	A61K31/425	C07D413/10
	C07D407/10	C07D209/12	A61K31/40	C07D409/10	C07D407/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TIDWELL R.R. ET AL.: "Diarylamidine derivatives with one or both of the aryl moieties consisting of an indole or indole-like ring. Inhibitors of arginine-specific esteroproteases" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 21, no. 7, 1 July 1978 (1978-07-01), pages 613-623, XP000573913 ISSN: 0022-2623 the whole document</p> <p>---</p> <p style="text-align: center;">-/--</p>	4-16

Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

28. 06. 00

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 99/30302

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07F9/09 A61K31/66 // (C07D471/04, 235:00, 221:00)

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Minimum documentation searched (classification system followed by classification symbols)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 114, no. 21, 27 May 1991 (1991-05-27) Columbus, Ohio, US; abstract no. 207259j, NISHI T. ET AL.: "Preparation of benzothiazoles and benzimidazoles as blood platelet aggregation inhibitors" page 832; column 1; XP002139445 abstract & JP 02 306916 A (OTSUKA PHARMACEUTICAL CO., LTD.; JAPAN) compounds 86-91 page 148 -page 149; table 2</p> <p style="text-align: center;">-/-</p>	4,6,9-11

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

Name and mailing address of the ISA

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Hartrampf, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/30302

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IWANOWICZ E.J. ET AL.: "Derivatives of 5-amidine indole as inhibitors of thrombin catalytic activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 6, no. 12, 18 June 1996 (1996-06-18), pages 1339-1344, XP004134837 ISSN: 0960-894X scheme 1 table 1 ----	12,13, 15,16
X	WO 98 22619 A (ARRIS PHARMACEUTICAL CORPORATION & REGENTS OF UNIVERSITY OF CALIFORNIA) 28 May 1998 (1998-05-28) claims 32-44,48,52,54 ----	4-16
P,X	WO 99 26933 A (AXYS PHARMACEUTICALS, INC.) 3 June 1999 (1999-06-03) compounds 22, 23 page 34; claims 1-7,9-11 ----	4-7, 9-13,15, 16
A	KATZ B.A. ET AL.: "Design of potent selective zinc-mediated serine protease inhibitors" NATURE, GB, MACMILLAN JOURNALS LTD. LONDON, vol. 391, 5 February 1998 (1998-02-05), pages 608-612, XP002095430 ISSN: 0028-0836 compounds APD-4, APD-6, APD-8 ----	4-16
P,A	WO 99 26941 A (AXYS PHARMACEUTICALS, INC.) 3 June 1999 (1999-06-03) compounds 1-7, 12-14, 18, 24-26, 28-30, 37, 42, 48-69, 84-88, 103-106, 108-110, 114-117 claims 1-8 -----	4-16

INTERNATIONAL SEARCH REPORT

Int'l. application No.
PCT/US 99/30302

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-3 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3

Due to the fact that the definition of the compounds of formula (I) is too general and/or encompasses too broad a range of different chemical groups (only partly supported by examples given in the description), the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (cf. Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.

Therefore the search was performed on the basis of the examples and those claims derived therefrom which are clear and concise, in combination with the alleged pharmaceutical use as protease inhibitors. The search report thus covers those compounds of formula (I) wherein A denotes either a benzimidazole or an indole moiety attached in 2-position to B being a substituted phenyl moiety, see claims 4, 5, 6(part), 7(part), 8, 12, 13 and 14 in combination with claims 11 or 16.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. onal Application No

PCT/US 99/30302

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
JP 2306916	A	20-12-1990	JP	2869561 B		10-03-1999
WO 9822619	A	28-05-1998	AU EP	2336497 A 0943008 A		10-06-1998 22-09-1999
WO 9926933	A	03-06-1999	AU	1608399 A		15-06-1999
WO 9926941	A	03-06-1999	AU	1607299 A		15-06-1999

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